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**WO 02/100341 A2**

(54) Title: COMPOUNDS FOR THE TREATMENT OF METABOLIC DISORDERS

(57) Abstract: Compounds useful for the treatment of various metabolic disorders, such as insulin resistance syndrome, diabetes, hyperlipidemia, fatty liver disease, cachexia, obesity, atherosclerosis and arteriosclerosis, are disclosed.

## COMPOUNDS FOR THE TREATMENT OF METABOLIC DISORDERS

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Diabetes mellitus is a major cause of morbidity and mortality. Chronically elevated blood glucose leads to debilitating complications: nephropathy, often necessitating dialysis or renal transplant; peripheral neuropathy; retinopathy leading to blindness; ulceration of the legs and feet, leading to amputation; fatty liver disease, sometimes progressing to cirrhosis; and vulnerability to coronary artery disease and myocardial infarction.

There are two primary types of diabetes. Type I, or insulin-dependent diabetes mellitus (IDDM) is due to autoimmune destruction of insulin-producing beta cells in the pancreatic islets. The onset of this disease is usually in childhood or adolescence. Treatment consists primarily of multiple daily injections of insulin, combined with frequent testing of blood glucose levels to guide adjustment of insulin doses, because excess insulin can cause hypoglycemia and consequent impairment of brain and other functions.

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Type II, or noninsulin-dependent diabetes mellitus (NIDDM) typically develops in adulthood. NIDDM is associated with resistance of glucose-utilizing tissues like adipose tissue, muscle, and liver, to the actions of insulin. Initially, the pancreatic islet beta cells compensate by secreting excess insulin. Eventual islet failure results in decompensation and chronic hyperglycemia. Conversely, moderate islet insufficiency can precede or coincide with peripheral insulin resistance. There are several classes of drugs that are useful for treatment of NIDDM: 1) insulin releasers, which directly

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stimulate insulin release, carrying the risk of hypoglycemia; 2) prandial insulin  
releasers, which potentiate glucose-induced insulin secretion, and must be taken before  
each meal; 3) biguanides, including metformin, which attenuate hepatic  
gluconeogenesis (which is paradoxically elevated in diabetes); 4) insulin sensitizers, for  
5 example the thiazolidinedione derivatives rosiglitazone and pioglitazone, which  
improve peripheral responsiveness to insulin, but which have side effects like weight  
gain, edema, and occasional liver toxicity; 5) insulin injections, which are often  
necessary in the later stages of NIDDM when the islets have failed under chronic  
hyperstimulation.

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Insulin resistance can also occur without marked hyperglycemia, and is generally  
associated with atherosclerosis, obesity, hyperlipidemia, and essential hypertension.  
This cluster of abnormalities constitutes the "metabolic syndrome" or "insulin  
resistance syndrome". Insulin resistance is also associated with fatty liver, which can  
15 progress to chronic inflammation (NASH; "nonalcoholic steatohepatitis"), fibrosis, and  
cirrhosis. Cumulatively, insulin resistance syndromes, including but not limited to  
diabetes, underlie many of the major causes of morbidity and death of people over age  
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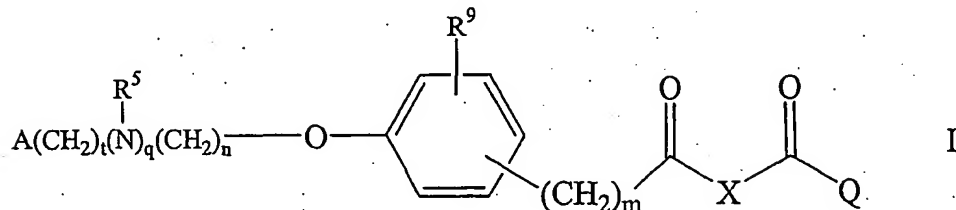
Despite the existence of such drugs, diabetes remains a major and growing public  
health problem. Late stage complications of diabetes consume a large proportion of  
national health care resources. There is a need for new orally active therapeutic agents  
which effectively address the primary defects of insulin resistance and islet failure with  
fewer or milder side effects than existing drugs.

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Currently there are no safe and effective treatments for fatty liver disease. Therefore  
such a treatment would be of value in treating this condition.

## SUMMARY OF THE INVENTION

This invention provides a biologically active agent, wherein the agent is a compound of the formula:



wherein  $n$  is 1 or 2;  $m$  is 0 or 1;  $q$  is 0 or 1;  $t$  is 0 or 1;  $R^5$  is alkyl having from 1 to 3 carbon atoms;  $R^9$  is hydrogen, halo, or alkoxy having from 1 to 3 carbon atoms;  $A$  is phenyl, unsubstituted or substituted by 1 or 2 groups selected from: halo, alkyl having 1 or 2 carbon atoms, perfluoromethyl, alkoxy having 1 or 2 carbon atoms, and perfluoromethoxy; or cycloalkyl having from 3 to 6 ring carbon atoms wherein the cycloalkyl is unsubstituted or one or two ring carbons are independently mono-substituted by methyl or ethyl; or a 5 or 6 membered heteroaromatic ring having 1 or 2 ring heteroatoms selected from N, S and O and the heteroaromatic ring is covalently bound to the remainder of the compound of formula I by a ring carbon; and  $X$  is  $-\text{CH}_2-$ ,  $Q$  is  $-\text{OR}^1$  and  $R^1$  is ethyl; or  $X$  is  $-\text{CH}_2\text{CR}^{12}\text{R}^{13}-$  or  $-\text{CH}_2\text{CH}(\text{NHAc})-$  wherein each of  $R^{12}$  and  $R^{13}$  is independently hydrogen or methyl,  $Q$  is  $\text{OR}^1$  and  $R^1$  is hydrogen or alkyl having from 1 to 7 carbon atoms; or  $X$  is  $-\text{CH}_2\text{CH}_2-$  and  $Q$  is  $\text{NR}^{10}\text{R}^{11}$  wherein one of  $R^{10}$  and  $R^{11}$  is hydrogen, alkyl having from 1 to 3 carbon atoms or hydroxy, and the other is hydrogen or alkyl having from 1 to 3 carbon atoms; or when  $R^1$  is hydrogen, a pharmaceutically acceptable salt of the compound.

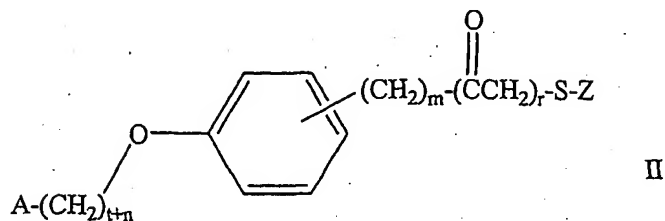
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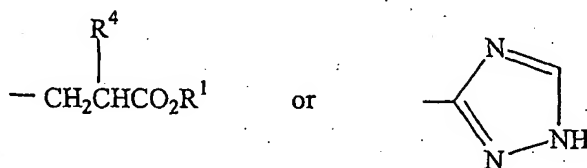
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This invention provides a biologically active agent, wherein the agent is a compound of the formula:

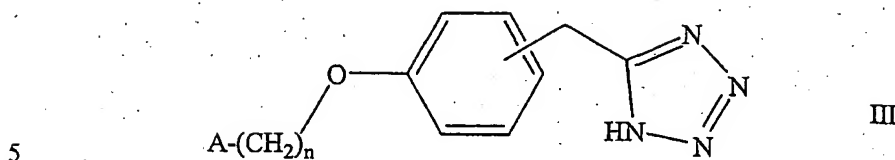


wherein n is 1 or 2; t is 0 or 1; m is 0 and r is 1, or m is 1 and r is 0; A is phenyl, unsubstituted or substituted by 1 or 2 groups selected from: halo, alkyl having 1 or 2 carbon atoms, perfluoromethyl, alkoxy having 1 or 2 carbon atoms, and perfluoromethoxy; or cycloalkyl having from 3 to 6 ring carbon atoms wherein the cycloalkyl is unsubstituted or one or two ring carbons are mono-substituted by methyl or ethyl; or a 5 or 6 membered heteroaromatic ring having 1 or 2 ring heteroatoms selected from N, S and O and the heteroaromatic ring is covalently bound to the remainder of the compound of formula II by a ring carbon; Z is



$R^1$  is hydrogen or alkyl having from 1 to 7 carbon atoms;  $R^4$  is hydrogen;  $-NHCOOC(CH_3)_3$ ;  $-NHCH_3$ ; or  $-NHCH_2CH_3$ ; or when  $R^1$  is hydrogen, a pharmaceutically acceptable salt of the compound.

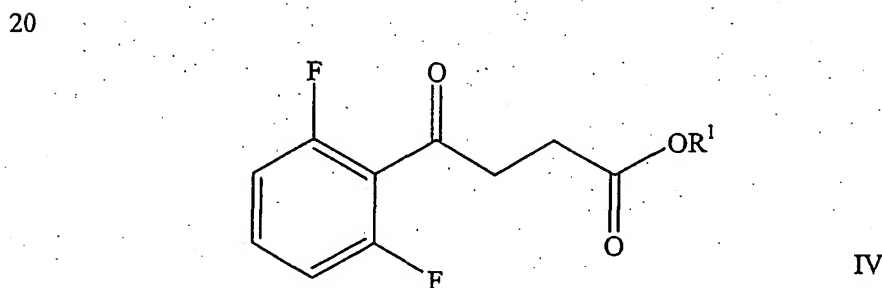
This invention provides a biologically active agent, wherein the agent is a compound of the formula:



wherein

- 10 n is 1 or 2; A is phenyl, unsubstituted or substituted by 1 or 2 groups selected from: halo, alkyl having 1 or 2 carbon atoms, perfluoromethyl, alkoxy having 1 or 2 carbon atoms, and perfluoromethoxy; or cycloalkyl having from 3 to 6 ring carbon atoms wherein one or both ring carbons are independently mono-substituted by methyl or ethyl; or a 5 or 6 membered heteroaromatic ring having 1 or 2 ring heteroatoms  
 15 selected from N, S and O and the heteroaromatic ring is covalently bound to the remainder of the compound of formula III by a ring carbon.

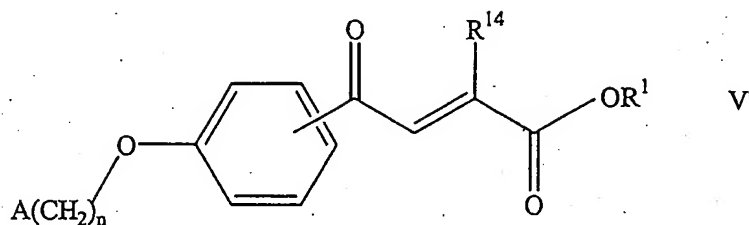
This invention provides a biologically active agent, wherein the agent is a compound of the formula:



wherein R<sup>1</sup> is hydrogen or alkyl having from 1 to 7 carbon atoms; or when R<sup>1</sup> is hydrogen, a pharmaceutically acceptable salt of the compound.

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This invention provides a biologically active agent, wherein the agent is a compound of the formula:

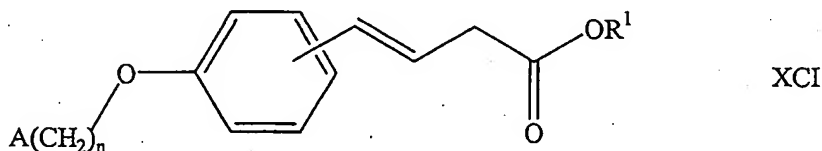


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- wherein  $n$  is 1 or 2;  $R^1$  is hydrogen or alkyl having from 1 to 7 carbon atoms;  $R^{14}$  is hydroxy or hydrogen; and  $A$  is phenyl, unsubstituted or substituted by 1 or 2 groups selected from halo, alkyl having 1 or 2 carbon atoms, perfluoromethyl, alkoxy having 1 or 2 carbon atoms, and perfluoromethoxy; or cycloalkyl having from 3 to 6 ring carbon atoms wherein the cycloalkyl is unsubstituted or one or two ring carbons are independently mono-substituted by methyl or ethyl; or a 5 or 6 membered heteroaromatic ring having 1 or 2 ring heteroatoms selected from N, S and O and the heteroaromatic ring is covalently bound to the remainder of the compound of formula I by a ring carbon;
- 15 or a pharmaceutically acceptable salt of the compound.

This invention provides a biologically active agent, wherein the agent is a compound of the formula:

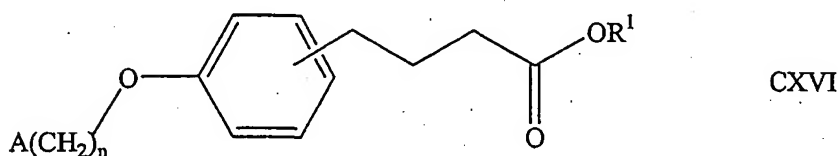
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- wherein  $n$  is 1 or 2;  $R^1$  is hydrogen or alkyl having from 1 to 3 carbon atoms; and  $A$  is phenyl, unsubstituted or substituted by 1 or 2 groups selected from halo, alkyl having 1 or 2 carbon atoms, perfluoromethyl, alkoxy having 1 or 2 carbon atoms, and perfluoromethoxy; or cycloalkyl having from 3 to 6 ring carbon atoms wherein the cycloalkyl is unsubstituted or one or two ring carbons are independently mono-substituted by methyl or ethyl; or a 5 or 6 membered heteroaromatic ring having 1 or 2
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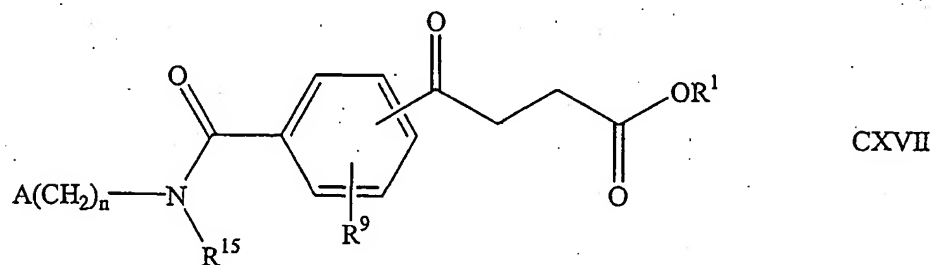
ring heteroatoms selected from N, S and O and the heteroaromatic ring is covalently bound to the remainder of the compound of formula I by a ring carbon; or a pharmaceutically acceptable salt of the compound.

This invention provides a biologically active agent, wherein the agent is a compound of the formula:



wherein n is 1 or 2;  $R^1$  is hydrogen or alkyl having from 1 to 3 carbon atoms; and A is phenyl, unsubstituted or substituted by 1 or 2 groups selected from halo, alkyl having 1 or 2 carbon atoms, perfluoromethyl, alkoxy having 1 or 2 carbon atoms, and perfluoromethoxy; or cycloalkyl having from 3 to 6 ring carbon atoms wherein the cycloalkyl is unsubstituted or one or two ring carbons are independently mono-substituted by methyl or ethyl; or a 5 or 6 membered heteroaromatic ring having 1 or 2 ring heteroatoms selected from N, S and O and the heteroaromatic ring is covalently bound to the remainder of the compound of formula I by a ring carbon; or a pharmaceutically acceptable salt of the compound.

This invention provides a biologically active agent, wherein the agent is a compound of the formula:



wherein n is 0, 1 or 2;  $R^1$  is hydrogen or alkyl having from 1 to 3 carbon atoms;  $R^{15}$  is hydrogen or alkyl having from 1 to 3 carbon atoms;  $R^9$  is hydrogen, halo, hydroxy, or alkoxy having from 1 to 3 carbon atoms; A is phenyl, unsubstituted or substituted by 1 or 2 groups selected from halo, alkyl having 1 or 2 carbon atoms, perfluoromethyl,

alkoxy having 1 or 2 carbon atoms, and perfluoromethoxy; or cycloalkyl having from 3 to 6 ring carbon atoms wherein the cycloalkyl is unsubstituted or one or two ring carbons are independently mono-substituted by methyl or ethyl; or a 5 or 6 membered heteroaromatic ring having 1 or 2 ring heteroatoms selected from N, S and O and the  
5 heteroaromatic ring is covalently bound to the remainder of the compound of formula I by a ring carbon; or a pharmaceutically acceptable salt of the compound.

The biologically active agents described above have activity in one or more of the biological activity assays described below, which are established animal models of  
10 human diabetes and insulin resistance syndrome. Therefore such agents would be useful in the treatment of diabetes and insulin resistance syndrome. All of the exemplified compounds that were tested demonstrated activity in the biological activity assay or assays in which they were tested.

15 This invention provides the use of the biologically active agents described above in the manufacture of a medicament for the treatment of insulin resistance syndrome, diabetes, cachexia, hyperlipidemia, fatty liver disease, obesity, atherosclerosis or arteriosclerosis. This invention also provides methods of treating a mammalian subject with insulin resistance syndrome, diabetes, cachexia, hyperlipidemia, fatty liver  
20 disease, obesity, atherosclerosis or arteriosclerosis comprising administering to the subject an effective amount of a biologically active agent in accordance with this invention. This invention also provides a pharmaceutical composition comprising a biologically active agent of this invention and a pharmaceutically acceptable carrier.

25 This invention provides certain novel intermediates, which are useful in producing the biologically active agents of this invention. The invention also provides processes of producing the biologically active agents and intermediates.

#### BRIEF DESCRIPTION OF THE FIGURES

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Figure 1: Serum insulin levels in high fat-fed C57B1/6J mice receiving vehicle (negative control), Compound BI, Compound BL, Wy14643 or rosiglitazone.

Figure 2: Serum leptin levels in high fat-fed C57B1/6J mice receiving vehicle (negative control), Compound BI, Compound BL, Wy14643 or rosiglitazone.

## 5 DETAILED DESCRIPTION OF THE INVENTION

### DEFINITIONS

As used herein the term "alkyl" means a linear or branched-chain alkyl group. An alkyl group identified as having a certain number of carbon atoms means any alkyl group  
 10 having the specified number of carbons. For example, an alkyl having three carbon atoms can be propyl or isopropyl; and alkyl having four carbon atoms can be n-butyl, 1-methylpropyl, 2-methylpropyl or t-butyl.

15 As used herein the term "halo" refers to one or more of fluoro, chloro, bromo, and iodo.

As used herein the term "perfluoro" as in perfluoromethyl or perfluoromethoxy, means that the group in question has fluorine atoms in place of all of the hydrogen atoms.

20 As used herein "Ac" refers to the group  $\text{CH}_3\text{C}(\text{O})-$ .

Examples of the biologically active compounds of the instant invention are listed below. These compounds are referred to herein by their chemical name or by the two-letter code shown below.

25

- AA 4-(4-(2-Fluorobenzyloxy)phenyl)-4-oxobutyric acid;
- AB 4-(4-(2-Methoxybenzyloxy)phenyl)-4-oxobutyric acid;
- AC 3-[(4-(2-Fluorobenzyloxy)phenyl)-methylthio]propionic acid;
- AD 4-(4-(3-Fluorobenzyloxy)phenyl)-4-oxobutyric acid;
- 30 AE 4-(4-(4-Fluorobenzyloxy)phenyl)-4-oxobutyric acid;
- AF 4-(4-((2-Pyridinyl)-methoxy)phenyl)-4-oxobutyric acid;
- AG 4-(4-(Benzyloxy)phenyl)-4-oxobutyric acid;
- AH 4-(4-(2,6-Difluorobenzyloxy)phenyl)-4-oxobutyric acid;
- AI 4-(4-(2-Chlorobenzyloxy)phenyl)-4-oxobutyric acid;

- AJ 4-(4-(2-(2-Fluorophenyl)ethoxy)phenyl)-4-oxobutyric acid;
- AK Ethyl 4-(4-(2-fluorobenzyloxy)phenyl)-4-oxobutyrate;
- AL 4-(4-(2-Methylbenzyloxy)phenyl)-4-oxobutyric acid;
- AM 4-[4-(2-(N-(2-fluorobenzyl)-N-methylamino)ethoxy)phenyl]-4-oxobutyric acid;
- 5 AN 4-(3-(2-Methylbenzyloxy)phenyl)-4-oxobutyric acid;
- AO Ethyl 4-(3-(2-fluorobenzyloxy)phenyl)-4-oxobutyrate;
- AP Ethyl 4-(4-(2-methylbenzyloxy)phenyl)-4-oxobutyrate;
- AQ Ethyl 4-(4-(2,6-difluorobenzyloxy)phenyl)-4-oxobutyrate;
- AR 4-(4-(2-(2-Thienyl)ethoxy)phenyl)-4-oxobutyric acid;
- 10 AS 4-(2,6-Difluorophenyl)-4-oxobutyric acid;
- AT 4-(4-(2,5-Dimethylbenzyloxy)phenyl)-4-oxobutyric acid;
- AU 4-(4-(2,5-Difluorobenzyloxy)phenyl)-4-oxobutyric acid;
- AV 4-(4-(2,4-Difluorobenzyloxy)phenyl)-4-oxobutyric acid;
- AW 4-(3-(2,6-Difluorobenzyloxy)phenyl)-4-oxobutyric acid;
- 15 AX 4-(4-((Cyclopropyl)-methoxy)phenyl)-4-oxobutyric acid;
- AY 4-(4-(2-Trifluoromethylbenzyloxy)phenyl)-4-oxobutyric acid;
- AZ 3-[(4-(2,6-Difluorobenzyloxy)phenyl)-methylthio]propionic acid;
- BA 4-(2-(2,6-Difluorobenzyloxy)phenyl)-4-oxobutyric acid;
- BB Ethyl 4-(4-(2,6-difluorobenzyloxy)phenyl)methyl-3-oxobutyrate;
- 20 BC 3-(2-(4-(2,6-Difluorobenzyloxy)phenyl)-2-oxoethyl)thio-(1H-1,2,4)-triazole;
- BD 5-[(4-(2,6-Difluorobenzyloxy)phenyl)-methyl]-1H-tetrazole;
- BE (2RS) 2-(N-Boc)-3-[2-(4-(2,6-difluorobenzyloxy)phenyl)-2-oxoethyl]  
thiopropionic acid;
- BF Ethyl 2-Hydroxy-4-oxo-4-(4-(2,6-difluorobenzyloxy)phenyl) but-2-enoate;
- 25 BG (2RS) 2-(N-Acetyl)-4-(4-(2,6-difluorobenzyloxy)phenyl)-4-oxobutyric acid;
- BH 4-(3-((Cyclopropyl)-methoxy)phenyl)-4-oxobutyric acid;
- BI 4-(3-(2,6-Dimethylbenzyloxy)phenyl)-4-oxobutyric acid;
- BJ 4-(3-(2-Fluoro-6-methylbenzyloxy)phenyl)-4-oxobutyric acid;
- BK Ethyl 4-(3-(2,6-dimethylbenzyloxy)phenyl)-4-oxobutyrate;
- 30 BL 4-(3-(2,6-Dimethylbenzyloxy)phenyl)-4-oxobutyric acid Sodium salt;
- BM 4-(4-(2,6-Dimethylbenzyloxy)phenyl)-4-oxobutyric acid;
- BN 4-(3-(2,6-Dimethylbenzyloxy)phenyl)-4-oxobutyric acid Potassium salt;
- BO 4-(3-(2,6-Dimethoxybenzyloxy)phenyl)-4-oxobutyric acid;
- BP 4-(3-(2,6-Dimethylbenzyloxy)phenyl)-4-oxo-2,2-dimethylbutyric acid;

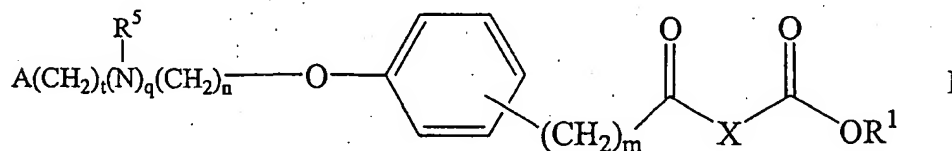
- BQ 4-(3-(4-Trifluoromethylbenzyloxy)phenyl)-4-oxobutyric acid;  
 BR 4-(3-((Cyclobutyl)-methoxy)phenyl)-4-oxobutyric acid;  
 BS 4-(3-(2,6-Dimethylbenzyloxy)phenyl)butyric acid;  
 BT 4-[[4-(2,6-Dimethylbenzyloxy)-3-methoxy]phenyl]-4-oxobutyric acid;  
 5 BU 4-[5-[[N-(4-Trifluoromethylbenzyl)aminocarbonyl]-2-methoxy]phenyl]-4-oxobutyric acid;  
 BV 4-[5-[[N-(2,6-Dimethylbenzyl)aminocarbonyl]-2-methoxy]phenyl]-4-oxobutyric acid;  
 BW 4-(3-(2,6-Dimethylbenzyloxy)phenyl)-4-oxobutanecarbohydroxamic acid;  
 10 BX 4-(3-(2,6-Dimethylbenzyloxy)phenyl)-4-oxobutyramide;  
 BY 4-(3-(2,6-Dimethylbenzyloxy)phenyl)-4-oxo-2-butenic acid; and  
 BZ 4-(3-(2,6-Dimethylbenzyloxy)phenyl)-3-butenic acid.

As used herein the transitional term "comprising" is open-ended. A claim utilizing this  
 15 term can contain elements in addition to those recited in such claim.

#### DETAILED DESCRIPTION OF ACTIVE COMPOUNDS

In an embodiment of the agent of Formula I', the agent is a compound of the formula:

20



wherein n is 1 or 2; m is 0 or 1; q is 0 or 1; t is 0 or 1; R<sup>5</sup> is alkyl having from 1 to 3  
 25 carbon atoms; A is phenyl, unsubstituted or substituted by 1 or 2 groups selected from:  
 halo, alkyl having 1 or 2 carbon atoms, perfluoromethyl, alkoxy having 1 or 2 carbon  
 atoms, and perfluoromethoxy; or cycloalkyl having from 3 to 6 ring carbon atoms  
 wherein the cycloalkyl is unsubstituted or one or two ring carbons are independently  
 mono-substituted by methyl or ethyl; or a 5 or 6 membered heteroaromatic ring having  
 30 1 or 2 ring heteroatoms selected from N, S and O and the heteroaromatic ring is  
 covalently bound to the remainder of the compound of formula I by a ring carbon; and



X is  $-\text{CH}_2-$  and  $\text{R}^1$  is ethyl; or X is  $-\text{CH}_2\text{CH}_2-$  or  $-\text{CH}_2\text{CH}(\text{NHAc})-$  and  $\text{R}^1$  is hydrogen or alkyl having from 1 to 7 carbon atoms; or when  $\text{R}^1$  is hydrogen, a pharmaceutically acceptable salt of the compound.

In different embodiments of the agent of Formula I,  $\text{R}^1$  is hydrogen or ethyl; q is 0; or

5 X is  $-\text{CH}_2\text{CH}_2-$ .

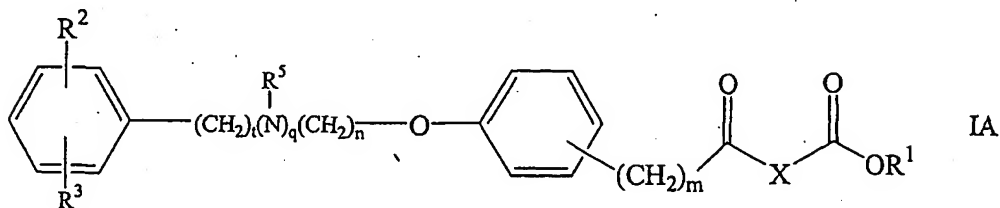
In another embodiment of the agent of Formula I, A is phenyl, unsubstituted or substituted by 1 or 2 groups selected from: halo, alkyl having 1 or 2 carbon atoms, perfluoromethyl, alkoxy having 1 or 2 carbon atoms, and perfluoromethoxy each halo is independently fluoro or chloro. In a specific embodiment each halo substituent on phenyl ring A is fluoro. In a more specific embodiment phenyl ring A is substituted by 2 fluoro groups. In a specific embodiment the alkyl, perfluoroalkyl, alkoxy or perfluoroalkoxy has 1 carbon atom.

10 In another embodiment of the agent of Formula I, A is cycloalkyl having from 3 to 6 ring carbon atoms wherein the cycloalkyl is unsubstituted or one or two ring carbons are independently mono-substituted by methyl or ethyl. In a specific embodiment the cycloalkyl is unsubstituted or one or both ring carbons adjacent to the ring carbon covalently bound to the remainder of the compound of formula I are independently mono-substituted by methyl or ethyl. In a more specific embodiment A is unsubstituted cyclopropyl.

In another embodiment of the agent of Formula I, q is 1 and  $\text{R}^5$  is methyl.

In another embodiment the agent is a compound of the formula:

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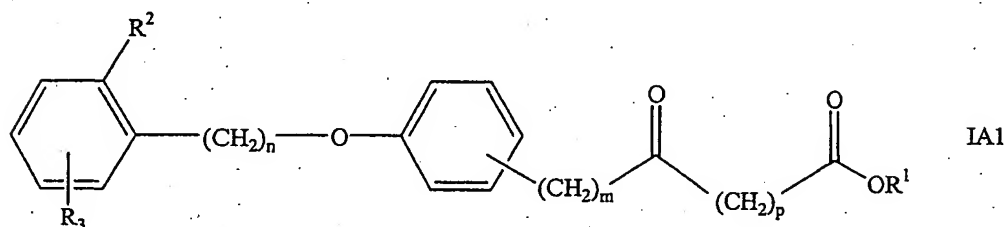
wherein n is 1 or 2; m is 0 or 1; q is 0 or 1; t is 0 or 1;  $\text{R}^2$  and  $\text{R}^3$  are each independently selected from hydrogen, halo, alkyl having 1 or 2 carbon atoms, perfluoromethyl,

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alkoxy having 1 or 2 carbon atoms, and perfluoromethoxy; R<sup>5</sup> is alkyl having from 1 to 3 carbon atoms; and X is -CH<sub>2</sub>- and R<sup>1</sup> is ethyl; or X is -CH<sub>2</sub>CH<sub>2</sub>- or -CH<sub>2</sub>CH(NHAc)- and R<sup>1</sup> is hydrogen or alkyl having from 1 to 7 carbon atoms; or when R<sup>1</sup> is hydrogen, a pharmaceutically acceptable salt of the compound. In a more specific embodiment R<sup>1</sup> is hydrogen or ethyl. Examples of compounds of Formula IA include Compound AM and Compound BG.

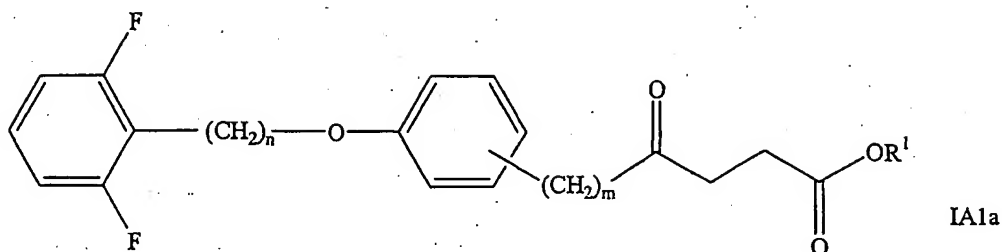
In a specific embodiment the agent is a compound of the formula:

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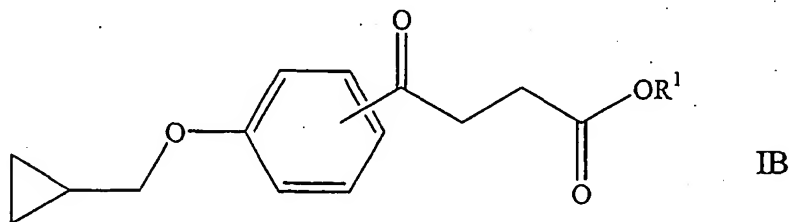
wherein n is 1 or 2; m is 0 or 1; p is 1 and R<sup>1</sup> is ethyl; or p is 2 and R<sup>1</sup> is hydrogen or alkyl having from 1 to 7 carbon atoms; R<sup>2</sup> and R<sup>3</sup> are each independently selected from hydrogen, halo, alkyl having 1 or 2 carbon atoms, perfluoromethyl, alkoxy having 1 or 2 carbon atoms, and perfluoromethoxy; or when R<sup>1</sup> is hydrogen, a pharmaceutically acceptable salt of the compound. In a more specific embodiment R<sup>1</sup> is hydrogen or ethyl. In a still more specific embodiment one of R<sup>2</sup> and R<sup>3</sup> is hydrogen or halo and the other is halo. Examples of such compounds include Compound AD, Compound AE and Compound AI. In another still more specific embodiment R<sup>2</sup> is fluoro and R<sup>3</sup> is hydrogen. Examples of such compounds include Compound AA, Compound AJ, Compound AK, and Compound AO. In another still more specific embodiment R<sup>2</sup> is fluoro and R<sup>3</sup> is fluoro. Examples of such compounds include Compound AU, Compound AV and Compound BB.

In a more specific embodiment the agent is a compound of the formula:



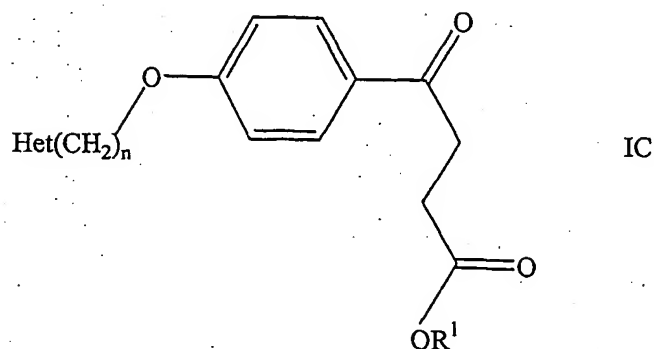
wherein n is 1 or 2; m is 0; R<sup>1</sup> is H or alkyl having from 1 to 7 carbon atoms; or when R<sup>1</sup> is hydrogen, a pharmaceutically acceptable salt of the compound. Examples of such compounds include Compound AH, Compound AQ, Compound AW and Compound BA. In a still more specific embodiment one of R<sup>2</sup> and R<sup>3</sup> is methyl, methoxy or perfluoromethyl and the other is hydrogen or methyl. In one embodiment R<sup>2</sup> is methyl, methoxy or perfluoromethyl and R<sup>3</sup> is hydrogen. Examples of such compounds include Compound AB, Compound AL, Compound AN, Compound AP and Compound AY. In another embodiment R<sup>2</sup> is methyl and R<sup>3</sup> is methyl. Examples of such compounds include Compound AT and Compound BI. In another embodiment R<sup>2</sup> is hydrogen and R<sup>3</sup> is hydrogen. Examples of such compounds include Compound AG.

In another embodiment the agent is a compound of the formula:



wherein R<sup>1</sup> is hydrogen or alkyl having from 1 to 7 carbon atoms, or when R<sup>1</sup> is hydrogen, a pharmaceutically acceptable salt of the compound. In a specific embodiment R<sup>1</sup> is hydrogen or ethyl. Examples of such compounds include Compound

AX and Compound BH. In another embodiment the agent is a compound of the formula:



5

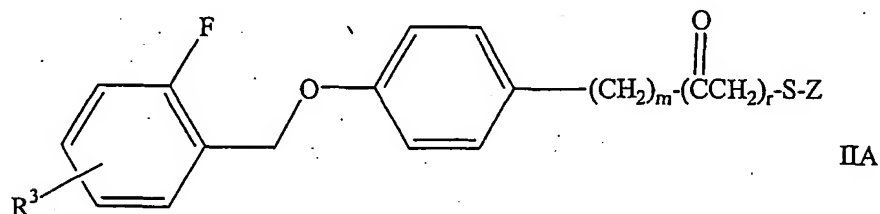
wherein  $n$  is 1 or 2;  $R^1$  is hydrogen or alkyl having from 1 to 7 carbon atoms; and Het is a 5 or 6 membered heteroaromatic ring having 1 or 2 ring heteroatoms selected from N, S and O and the heteroaromatic ring is covalently bound to the remainder of the compound of formula IC by a ring carbon. In a specific embodiment  $R^1$  is hydrogen or ethyl. Examples of such compounds include Compound AF and Compound AR.

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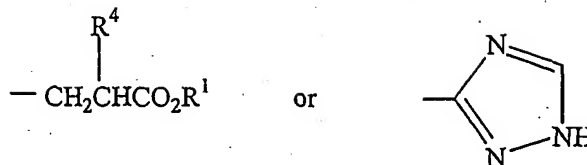
In an embodiment of the agent of Formula II, A is cycloalkyl having from 3 to 6 ring carbon atoms wherein the cycloalkyl is unsubstituted or one or both of the ring carbons adjacent to the remainder of the compound of formula II are mono-substituted by methyl or ethyl. In another embodiment of the agent of Formula II, A is phenyl, unsubstituted or substituted by 1 or 2 groups selected from: fluoro, alkyl having 1 or 2 carbon atoms, perfluoromethyl, alkoxy having 1 or 2 carbon atoms, and perfluoromethoxy.

15

20 In another embodiment, the agent is a compound of the formula:



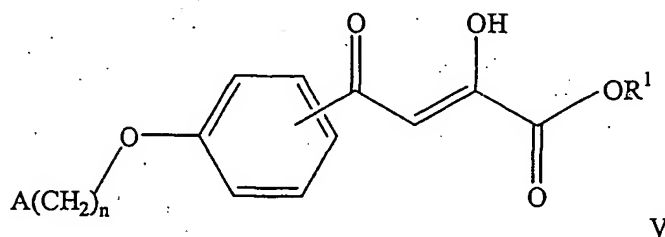
wherein m is 0 or 1; r is 0 or 1; Z is



- R<sup>1</sup> is hydrogen or alkyl having from 1 to 7 carbon atoms; R<sup>4</sup> is hydrogen;
- 5    -NHCOOC(CH<sub>3</sub>)<sub>3</sub>; -NHCH<sub>3</sub>; or -NHCH<sub>2</sub>CH<sub>3</sub>; R<sup>3</sup> is hydrogen or halo; or when R<sup>1</sup> is hydrogen, a pharmaceutically acceptable salt of the compound. In a specific embodiment R<sup>1</sup> is hydrogen or ethyl. Examples of such compounds include Compound AC, Compound AZ, Compound BC and Compound BE.
- 10    In an embodiment of the agent of Formula III, A is phenyl, unsubstituted or substituted by 1 or 2 groups selected from: halo, alkyl having 1 or 2 carbon atoms, perfluoromethyl, alkoxy having 1 or 2 carbon atoms, and perfluoromethoxy. Examples of such compounds include Compound BD.
- 15    In an embodiment of the agent of Formula IV, R<sup>1</sup> is hydrogen or ethyl. Examples of such compounds include Compound AS.

In an embodiment of the agent of Formula V', the agent is a compound of the formula:

20

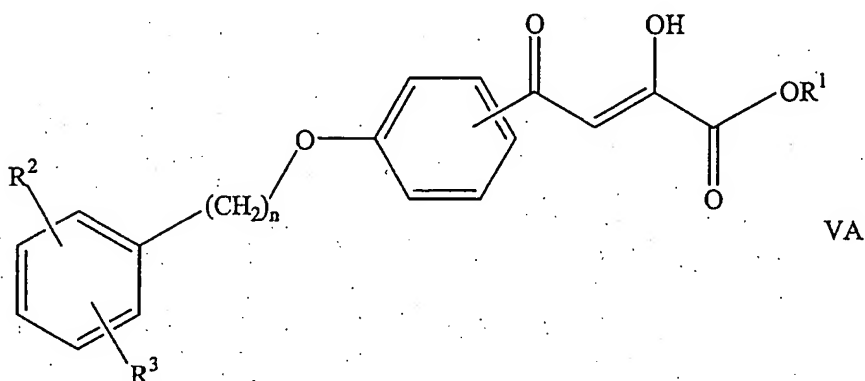


- wherein n is 1 or 2; R<sup>1</sup> is hydrogen or alkyl having from 1 to 7 carbon atoms; A is phenyl, unsubstituted or substituted by 1 or 2 groups selected from halo, alkyl having 1
- 25    or 2 carbon atoms, perfluoromethyl, alkoxy having 1 or 2 carbon atoms, and perfluoromethoxy; or cycloalkyl having from 3 to 6 ring carbon atoms wherein the cycloalkyl is unsubstituted or one or two ring carbons are independently mono-

substituted by methyl or ethyl; or a 5 or 6 membered heteroaromatic ring having 1 or 2 ring heteroatoms selected from N, S and O and the heteroaromatic ring is covalently bound to the remainder of the compound of formula I by a ring carbon; or a pharmaceutically acceptable salt of the compound.

5

In an embodiment of the agent of Formula V, the agent is a compound of the formula:



10 wherein n is 1 or 2; R¹ is hydrogen or alkyl having from 1 to 7 carbon atoms; R² and R³ are each independently selected from hydrogen, halo, alkyl having 1 or 2 carbon atoms, perfluoromethyl, alkoxy having 1 or 2 carbon atoms, and perfluoromethoxy, or a pharmaceutically acceptable salt of the compound. In a specific embodiment R¹ is hydrogen or ethyl. Examples of such compounds include Compound BF.

15

#### USE IN METHODS OF TREATMENT

This invention provides a method for treating a mammalian subject with a condition selected from the group consisting of insulin resistance syndrome and diabetes (both  
 20 primary essential diabetes such as Type I Diabetes or Type II Diabetes and secondary nonessential diabetes), comprising administering to the subject an amount of a biologically active agent as described herein effective to treat the condition. In accordance with the method of this invention a symptom of diabetes or the chance of developing a symptom of diabetes, such as atherosclerosis, obesity, hypertension,  
 25 hyperlipidemia, fatty liver disease, nephropathy, neuropathy, retinopathy, foot ulceration and cataracts, each such symptom being associated with diabetes, can be

reduced. This invention also provides a method for treating hyperlipidemia comprising administering to the subject an amount of a biologically active agent as described herein effective to treat the condition. As shown in the Examples, compounds reduce serum triglycerides and free fatty acids in hyperlipidemic animals. This invention also provides a method for treating cachexia comprising administering to the subject an amount of a biologically active agent as described herein effective to treat the cachexia. This invention also provides a method for treating obesity comprising administering to the subject an amount of a biologically active agent as described herein effective to treat the condition. This invention also provides a method for treating a condition selected from atherosclerosis or arteriosclerosis comprising administering to the subject an amount of a biologically active agent as described herein effective to treat the condition. The active agents of this invention are effective to treat hyperlipidemia, fatty liver disease, cachexia, obesity, atherosclerosis or arteriosclerosis whether or not the subject has diabetes or insulin resistance syndrome. The agent can be administered by any conventional route of systemic administration. Preferably the agent is administered orally. Other routes of administration that can be used in accordance with this invention include rectally, parenterally, by injection (e.g. intravenous, subcutaneous, intramuscular or intraperitoneal injection), or nasally.

Further embodiments of each of the uses and methods of treatment of this invention comprise administering any one of the embodiments of the biologically active agents described above. In the interest of avoiding unnecessary redundancy, each such agent and group of agents is not being repeated, but they are incorporated into this description of uses and methods of treatment as if they were repeated.

Many of the diseases or disorders that are addressed by the compounds of the invention fall into two broad categories: Insulin resistance syndromes and consequences of chronic hyperglycemia. Dysregulation of fuel metabolism, especially insulin resistance, which can occur in the absence of diabetes (persistent hyperglycemia) per se, is associated with a variety of symptoms, including hyperlipidemia, atherosclerosis, obesity, essential hypertension, fatty liver disease (NASH; nonalcoholic steatohepatitis), and, especially in the context of cancer or systemic inflammatory disease, cachexia. Cachexia can also occur in the context of Type I Diabetes or late-stage Type II

Diabetes. By improving tissue fuel metabolism, active agents of the invention are useful for preventing or ameliorating diseases and symptoms associated with insulin resistance, as is demonstrated in animals in the Examples. While a cluster of signs and symptoms associated with insulin resistance may coexist in an individual patient, it  
5 many cases only one symptom may dominate, due to individual differences in vulnerability of the many physiological systems affected by insulin resistance. Nonetheless, since insulin resistance is a major contributor to many disease conditions, drugs which address this cellular and molecular defect are useful for prevention or amelioration of virtually any symptom in any organ system that may be due to, or  
10 exacerbated by, insulin resistance.

When insulin resistance and concurrent inadequate insulin production by pancreatic islets are sufficiently severe, chronic hyperglycemia occurs, defining the onset of Type II diabetes mellitus (NIDDM). In addition to the metabolic disorders related to insulin  
15 resistance indicated above, disease symptoms secondary to hyperglycemia also occur in patients with NIDDM. These include nephropathy, peripheral neuropathy, retinopathy, microvascular disease, ulceration of the extremities, and consequences of nonenzymatic glycosylation of proteins, e.g. damage to collagen and other connective tissues. Attenuation of hyperglycemia reduces the rate of onset and severity of these  
20 consequences of diabetes. Because, as is demonstrated in the Examples, active agents and compositions of the invention help to reduce hyperglycemia in diabetes, they are useful for prevention and amelioration of complications of chronic hyperglycemia.

Both human and non-human mammalian subjects can be treated in accordance with the  
25 treatment method of this invention. The optimal dose of a particular active agent of the invention for a particular subject can be determined in the clinical setting by a skilled clinician. In the case of oral administration to a human for treatment of disorders related to insulin resistance, diabetes, hyperlipidemia, fatty liver disease, cachexia or obesity the agent is generally administered in a daily dose of from 1 mg to 400 mg,  
30 administered once or twice per day. For oral administration to a human the anticipated preferred daily dose of Compound AH is from 100 mg to 400 mg; of Compound AW is from 30 to 300 mg; and of Compound BI is from 10 to 200 mg. In the case of oral administration to a mouse the agent is generally administered in a daily dose from 1 to 300 mg of the agent per kilogram of body weight. Active agents of the invention are



- used as monotherapy in diabetes or insulin resistance syndrome, or in combination with one or more other drugs with utility in these types of diseases, e.g. insulin releasing agents, prandial insulin releasers, biguanides, or insulin itself. Such additional drugs are administered in accord with standard clinical practice. In some cases, agents of the invention will improve the efficacy of other classes of drugs, permitting lower (and therefore less toxic) doses of such agents to be administered to patients with satisfactory therapeutic results. Established safe and effective dose ranges in humans for representative compounds are: metformin 500 to 2550 mg/day; glyburide 1.25 to 20 mg/day; GLUCOVANCE (combined formulation of metformin and glyburide) 1.25 to 20 mg/day glyburide and 250 to 2000 mg/day metformin; atorvastatin 10 to 80 mg/day; lovastatin 10 to 80 mg/day; pravastatin 10 to 40 mg/day; and simvastatin 5-80 mg/day; clofibrate 2000 mg/day; gemfibrozil 1200 to 2400 mg/day, rosiglitazone 4 to 8 mg/day; pioglitazone 15 to 45 mg/day; acarbose 75-300 mg/day; repaglinide 0.5 to 16 mg/day.
- 15 Type I Diabetes Mellitus: A patient with Type I diabetes manages their disease primarily by self-administration of one to several doses of insulin per day, with frequent monitoring blood glucose to permit appropriate adjustment of the dose and timing of insulin administration. Chronic hyperglycemia leads to complications such as nephropathy, neuropathy, retinopathy, foot ulceration, and early mortality;
- 20 hypoglycemia due to excessive insulin dosing can cause cognitive dysfunction or unconsciousness. A patient with Type I diabetes is treated with 1 to 400 mg/day of an active agent of this invention, e.g. 50 to 400 mg/day of Compound AH, in tablet or capsule form either as a single or a divided dose. The anticipated effect will be a reduction in the dose or frequency of administration of insulin required to maintain
- 25 blood glucose in a satisfactory range, and a reduced incidence and severity of hypoglycemic episodes. Clinical outcome is monitored by measurement of blood glucose and glycosylated hemoglobin (an index of adequacy of glycemic control integrated over a period of several months), as well as by reduced incidence and severity of typical complications of diabetes. A biologically active agent of this
- 30 invention can be administered in conjunction with islet transplantation to help maintain the anti-diabetic efficacy of the islet transplant.

Type II Diabetes Mellitus: A typical patient with Type II diabetes (NIDDM) manages their disease by programs of diet and exercise as well as by taking medications such as

metformin, glyburide, repaglinide, rosiglitazone, or acarbose, all of which provide some improvement in glycemic control in some patients, but none of which are free of side effects or eventual treatment failure due to disease progression. Islet failure occurs over time in patients with NIDDM, necessitating insulin injections in a large fraction of patients. It is anticipated that daily treatment with an active agent of the invention (with or without additional classes of antidiabetic medication) will improve glycemic control, reduce the rate of islet failure, and reduce the incidence and severity of typical symptoms of diabetes. In addition, active agents of the invention will reduce elevated serum triglycerides and fatty acids, thereby reducing the risk of cardiovascular disease, a major cause of death of diabetic patients. Suitable daily dose ranges for selected compounds of the invention for treatment of NIDDM (either as monotherapy or in combination with other antidiabetic drugs) are from 50 mg to 400 mg of Compound AH, from 15 mg to 300 mg of Compound AW, or from 5 mg to 200 mg of Compound BI. As is the case for all other therapeutic agents for diabetes, dose optimization is done in individual patients according to need, clinical effect, and susceptibility to side effects.

Hyperlipidemia: Elevated triglyceride and free fatty acid levels in blood affect a substantial fraction of the population and are an important risk factor for atherosclerosis and myocardial infarction. Active agents of the invention are useful for reducing circulating triglycerides and free fatty acids in hyperlipidemic patients. Suitable daily dose ranges for selected compounds of the invention for treatment of hypertriglyceridemia are from 50 mg to 400 mg of Compound AH, from 15 mg to 300 mg of Compound AW, or from 5 mg to 200 mg of Compound BI. Hyperlipidemic patients often also have elevated blood cholesterol levels, which also increase the risk of cardiovascular disease. Cholesterol-lowering drugs such as HMG-CoA reductase inhibitors ("statins") can be administered to hyperlipidemic patients in addition to agents of the invention, optionally incorporated into the same pharmaceutical composition.

Fatty Liver Disease: A substantial fraction of the population is affected by fatty liver disease, also known as nonalcoholic steatohepatitis (NASH); NASH is often associated with obesity and diabetes. Hepatic steatosis, the presence of droplets of triglycerides with hepatocytes, predisposes the liver to chronic inflammation (detected in biopsy

samples as infiltration of inflammatory leukocytes), which can lead to fibrosis and cirrhosis. Fatty liver disease is generally detected by observation of elevated serum levels of liver-specific enzymes such as the transaminases ALT and AST, which serve as indices of hepatocyte injury, as well as by presentation of symptoms which include fatigue and pain in the region of the liver, though definitive diagnosis often requires a biopsy. As is shown in the Examples, compounds of the invention, e.g. Compound AW, reduce serum liver transaminases and liver fat content in an established animal model of NASH (ob/ob obese mice), and are therefore useful for treatment of fatty liver disease. An appropriate dose range of Compound AW for treatment of fatty liver disease is 15 to 300 mg/day. The anticipated benefit is a reduction in liver inflammation and fat content, resulting in attenuation, halting, or reversal of the progression of NASH toward fibrosis and cirrhosis.

#### PHARMACEUTICAL COMPOSITIONS

This invention provides a pharmaceutical composition comprising a biologically active agent as described herein and a pharmaceutically acceptable carrier. Further embodiments of the pharmaceutical composition of this invention comprise any one of the embodiments of the biologically active agents described above. In the interest of avoiding unnecessary redundancy, each such agent and group of agents is not being repeated, but they are incorporated into this description of pharmaceutical compositions as if they were repeated.

Preferably the composition is adapted for oral administration, e.g. in the form of a tablet, coated tablet, dragee, hard or soft gelatin capsule, solution, emulsion or suspension. In general the oral composition will comprise from 1 mg to 400 mg of such agent. It is convenient for the subject to swallow one or two tablets, coated tablets, dragees, or gelatin capsules per day. Accordingly, preferred oral compositions for treatment of humans comprise from 50 mg to 400 mg of Compound AH, from 15 mg to 300 mg of Compound AW, or from 5 mg to 200 mg of Compound BI. However the composition can also be adapted for administration by any other conventional means of systemic administration including rectally, e.g. in the form of suppositories, parenterally, e.g. in the form of injection solutions, or nasally.

The biologically active compounds can be processed with pharmaceutically inert, inorganic or organic carriers for the production of pharmaceutical compositions. Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts and the like can be used, for example, as such carriers for tablets, coated tablets, dragees and hard  
5 gelatin capsules. Suitable carriers for soft gelatin capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like. Depending on the nature of the active ingredient no carriers are, however, usually required in the case of soft gelatin capsules, other than the soft gelatin itself. Suitable carriers for the production of solutions and syrups are, for example, water, polyols, glycerol, vegetable oils and the  
10 like. Suitable carriers for suppositories are, for example, natural or hardened oils, waxes, fats, semi-liquid or liquid polyols and the like.

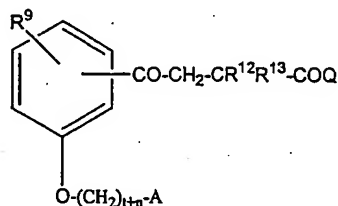
The pharmaceutical compositions can, moreover, contain preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for  
15 varying the osmotic pressure, buffers, coating agents or antioxidants. They can also contain still other therapeutically valuable substances, particularly antidiabetic or hypolipidemic agents that act through mechanisms other than those underlying the effects of the compounds of the invention. Agents which can advantageously be combined with compounds of the invention in a single formulation include but are not  
20 limited to biguanides such as metformin, insulin releasing agents such as the sulfonylurea insulin releaser glyburide and other sulfonylurea insulin releasers, cholesterol-lowering drugs such as the "statin" HMG-CoA reductase inhibitors such as atorvastatin, lovastatin, pravastatin and simvastatin, PPAR-alpha agonists such as clofibrate and gemfibrozil, PPAR-gamma agonists such as thiazolidinediones (e.g.  
25 rosiglitazone and pioglitazone, alpha-glucosidase inhibitors such as acarbose (which inhibit starch digestion), and prandial insulin releasers such as repaglinide. The amounts of complementary agents combined with compounds of the invention in single formulations are in accord with the doses used in standard clinical practice. Established safe and effective dose ranges for certain representative compounds are set forth above.

30

## REACTION SCHEMES

The biologically active compounds of the present invention can be made in accordance with the following reaction schemes.

The compound of formula I' where X is  $-\text{CH}_2\text{CR}^{12}\text{R}^{13}-$ , q and m are 0, t is 0 or 1, and n is 1 or 2,  $\text{R}^9$  is hydrogen, halo, or alkoxy having 1 to 3 carbon atoms, Q is  $\text{OR}^1$  where  $\text{R}^1$  is hydrogen or alkyl having from 1 to 7 carbons, i.e. compounds of formula:



wherein A is as described above, and  $\text{R}^1$  is hydrogen or alkyl having from 1 to 7 carbon atoms,  $\text{R}^{12}$  and  $\text{R}^{13}$  is independently hydrogen or methyl can be prepared from the compound of formula VI via the reaction scheme in Scheme 1.

In the reaction scheme of Scheme 1, A, t, n and  $\text{R}^9$  are as above.  $\text{R}^6$  is an alkyl group containing from 1 to 7 carbon atoms,  $\text{R}^{12}$  and  $\text{R}^{13}$  is independently hydrogen or methyl and Y is a leaving group.

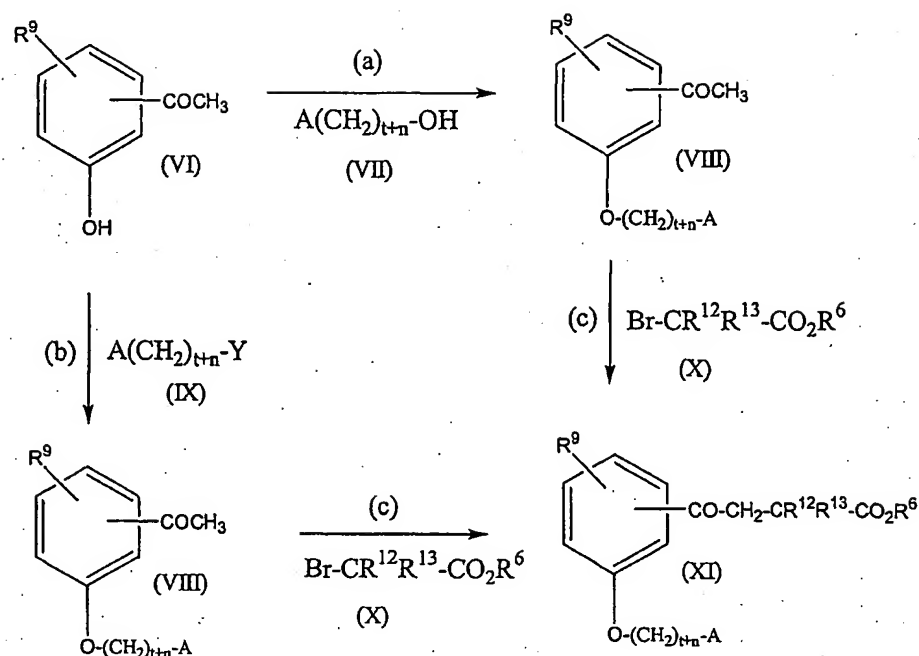
The compound of formula VI is converted to the compound of formula VIII via reaction of step (a) using Mitsunobu condensation of VI with VII using triphenylphosphine and diethyl azodicarboxylate. Any of the conditions conventionally used in Mitsunobu reactions can be utilized to carry out the reaction of step (a).

The compound of formula VIII can also be prepared by etherifying or alkylating the compound of formula VI with a compound of formula IX as in reaction of step (b). In the compound of formula IX, Y can be any conventional leaving group such as mesyloxy, tosyloxy or a halide. Any conventional method of etherifying of a hydroxyl group through reaction with a halide or leaving group can be utilized to carry out the reaction of step (b). The reaction of step (b) is preferred over step (a) if compound of formula IX is readily available.

The compound of formula VIII is converted to the compound of formula XI via reaction of step (c) by alkylating the compound of formula VIII with the compound of

- formula X. This reaction is carried out utilizing a conventional base which converts acetophenone to 3-keto ester (i.e. gamma-keto ester). Any conventional base for this purpose can be utilized in the reaction of step (c). In carrying out this reaction it is generally preferred to utilize alkali metal salts of hexamethyldisilazane such as lithium bis(trimethylsilyl)amide as base. Generally this reaction is carried out in an inert solvent such as tetrahydrofuran : 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (5:1). Any of the conditions conventional in such alkylation reactions can be utilized to carry out the reaction of step (c).
- 10 The compound of formula XI is the compound of formula I' where  $R^1$  is an alkyl group containing from 1 to 7 carbon atoms. The compound of formula XI can be converted to the free acid i.e. the compound of formula I' where  $R^1$  is H by ester hydrolysis. Any conventional method of ester hydrolysis will produce the compound of formula I' where  $R^1$  is H.
- 15 The compound of general formula VII can be prepared by reducing the corresponding acid of formula  $A-(CH_2)_{t+n}-CO_2H$ . The reaction is carried out first by esterification of compound of formula  $A-(CH_2)_{t+n}CO_2H$  with methyl iodide, followed by reduction utilizing a conventional base for example, lithium aluminium hydride or the like in an
- 20 inert organic solvent for example, tetrahydrofuran or the like. Any of the conditions conventional in such reduction reactions can be utilized to carry out this reaction.

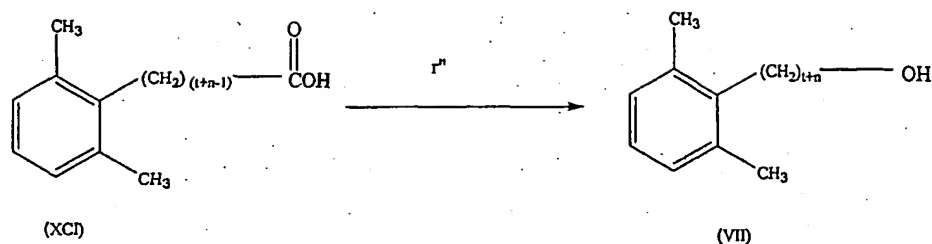
Scheme 1



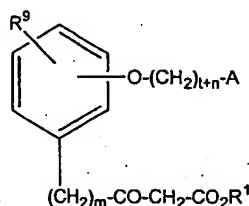
- 5 The compound of formula VII where A is 2,6 Dimethyl phenyl can be prepared from the compound of formula XCI, via the reaction scheme in Scheme 2.

In Scheme 2, the compound of formula XCI can be converted to compound of formula VII by esterification with methyl iodide, followed by reduction with lithium aluminum hydride via reaction of step (r''). The reaction of step (r'') can be carried out utilizing a conventional reducing agent. In carrying out this reaction it is generally preferred to utilize lithium aluminum hydride as the reducing agent. Any of the conditions conventional in reduction reactions can be utilized to carry out this reaction.

Scheme 2



- 5 The compound of formula I where X is  $-\text{CH}_2-$ , q is 0, m is 1, t is 0 or 1 and n is 1 or 2, i.e. compounds of the formula:



- 10 wherein A is as described above,  $\text{R}^1$  is ethyl, and  $\text{R}^9$  is hydrogen, halo, or alkoxy having 1 to 3 carbon atoms can be prepared from the compound of formula XII, wherein m is as above via the reaction scheme in Scheme 3.

In Scheme 3, A is as above, Y is a leaving group such as halide, mesyloxy or tosyloxy.

- 15  $\text{Y}^1$  is chloro.

In Scheme 3, the compound of formula XII is converted into the ethyl ester of formula XIII using ethanol via reaction of step (d). Any conventional method of converting acid to ethyl ester can be utilized to carry out this reaction.

20

The compound of formula XIII can be converted to compound of formula XIV in the same manner as described in the connection with reaction of step (a) or (b) hereinbefore.



In the step of (f), the compound of formula XIV is hydrolyzed to produce the compound of formula XV. Any conventional method of basic hydrolysis to hydrolyze ester can be utilized to carry out this reaction.

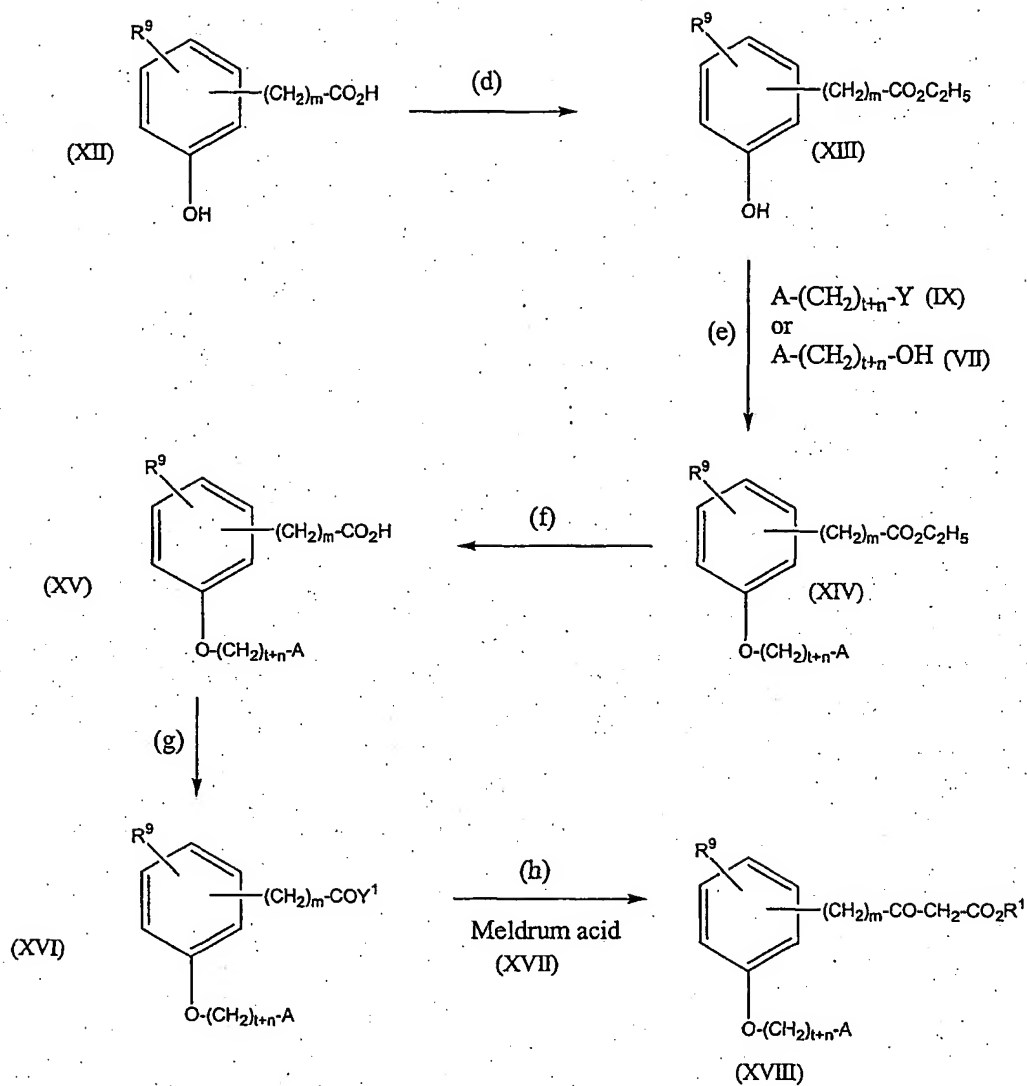
- 5    The compound of formula XV is converted to the acid chloride of formula XVI via reaction of step (g) by reaction with thionyl chloride. Any of the conventional methods of converting acid to acid halide can be utilized to carry out this reaction of step (g).

- 10    The compound of formula XVII is reacted with acid chloride of formula XVI to produce the compound of formula XVIII via reaction of step (h). Any conventional base can be utilized to carry out this reaction with the preferred base being pyridine. The resulting acylated Meldrum acids were not isolated, and instead after workup they were refluxed in absolute ethanol to give the 2-ketoesters. Any conventional conditions to carry out the reaction of step (h) can be utilized.

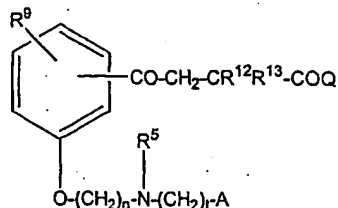
15

The compound of formula XVIII is the compound of formula I where R<sup>1</sup> is ethyl.

Scheme 3



The compound of formula I' where q is 1, R<sup>5</sup> is an alkyl group having 1 to 3 carbon atoms where X is -CH<sub>2</sub>CR<sup>12</sup>R<sup>13</sup>-, m is 0, t is 0 or 1 and n is 1 or 2, i.e. compounds of the formula:



5

wherein A is as above, R<sup>1</sup> is hydrogen or alkyl having from 1 to 7 carbon atoms, and R<sup>12</sup> and R<sup>13</sup> is independently hydrogen or methyl, R<sup>9</sup> is hydrogen, halo, or alkoxy having 1 to 3 carbon atoms, Q is OR<sup>1</sup> where R<sup>1</sup> is hydrogen or alkyl having from 1 to 7 carbons, can be prepared from the compound of formula XIX, wherein t and A are as above via the reaction scheme in Scheme 4.

10

In Scheme 4, t, n, A, R<sup>1</sup>, R<sup>9</sup>, R<sup>12</sup>, R<sup>13</sup> and R<sup>5</sup> are as above. R<sup>6</sup> is an alkyl group having 1 to 7 carbon atoms. Y<sup>1</sup> is chloro.

15

In Scheme 4, the compound of formula XIX is mesylated to furnish the compound of formula XX via reaction of step (i). Any conventional conditions to carry out mesylation can be utilized. The compound of formula XX is then heated with the compound of formula XXI to produce the compound of formula XXII. Any of the conditions conventional to produce amino alcohol can be utilized in reaction of step (j).

20

In the compound of formula XXII, alcohol is then displaced by chloro by treating the compound of formula XXII with thionyl chloride to produce compound of formula XXIII via reaction of step (k). Any conventional method to displace alcohol with halo can be utilized to carry out this reaction.

25

The compound of formula XXIII is reacted with a compound of formula VI in the presence of base using dimethylformamide as solvent via reaction of step (l) to produce the corresponding compound of formula XXIV. The position of the substituents in the compound of formula VI will determine the position of the substituents in the

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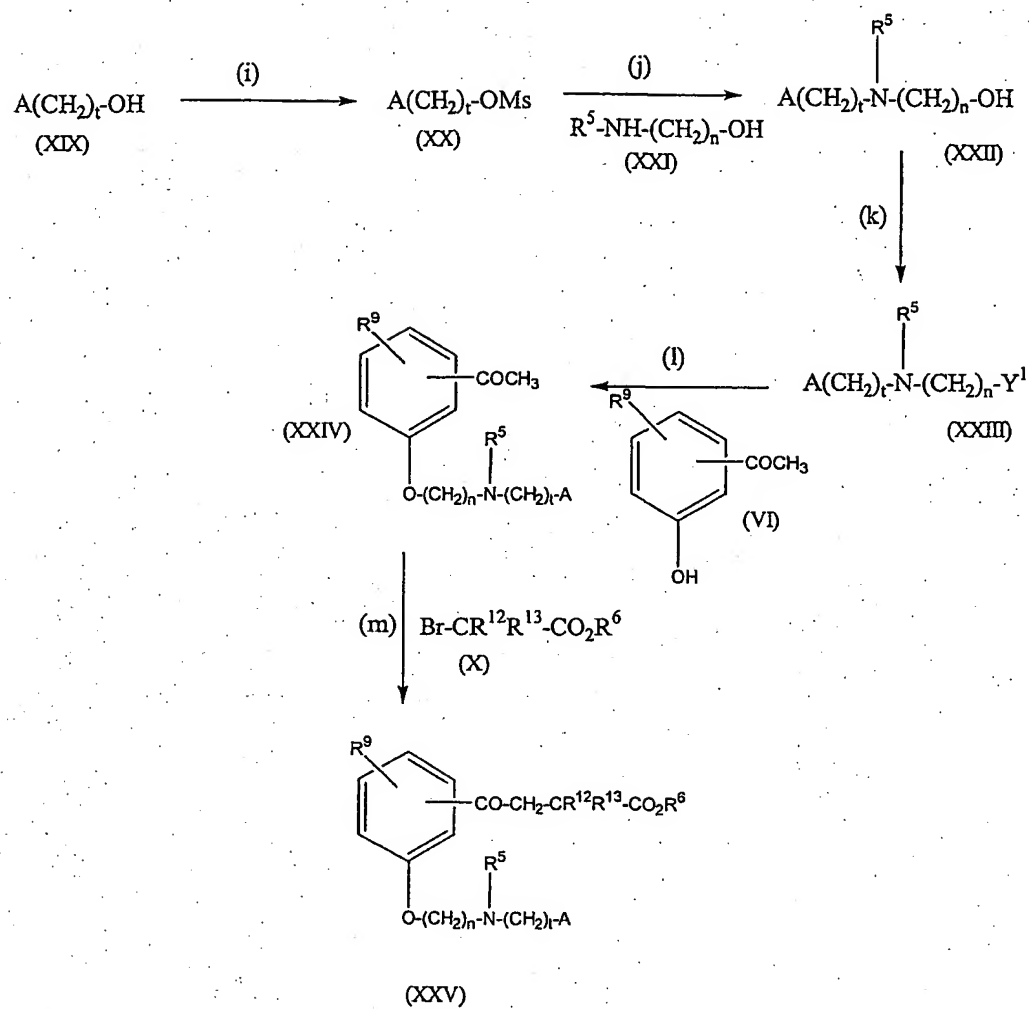
compound of formula XXIV. Any conventional method of etherification of a hydroxyl group in the presence of base (preferred base being potassium carbonate) with a halide can be utilized to carry out the reaction of step (l). The compound of formula XXIV is converted to the compound of formula XXV via reaction of step (m) by alkylating the

5 compound of formula XXIV with the compound of formula X in the presence of alkali metal silyl amide as base (eg. lithium hexamethyldisilane or sodium hexamethyldisilane). This reaction is carried out in the same manner as described in connection with reaction of step (c) of Scheme 1.

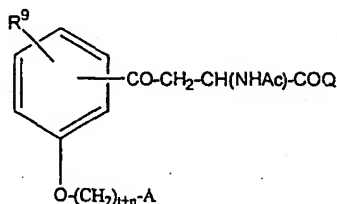
10 The compound of formula XXV is the compound of formula I' where  $R^1$  is an alkyl group having 1 to 7 carbon atoms. The compound of formula XXV can be converted to the free acid i.e. the compound of formula I' where  $R^1$  is H by ester hydrolysis. Any conventional method of ester hydrolysis will produce the compound of formula I' where  $R^1$  is H.

15

Scheme 4



The compound of formula I' where X is  $-\text{CH}_2\text{CH}(\text{NHAc})-$ , - m is 0, q is 0, t is 0 or 1 and n is 1 or 2, i.e. compounds of the formula:



5

wherein A is as above,  $\text{R}^1$  is hydrogen or alkyl having from 1 to 7 carbon atoms, and  $\text{R}^9$  is hydrogen, halo, or alkoxy having 1 to 3 carbon atoms, Q is  $\text{OR}^1$  where  $\text{R}^1$  is hydrogen or alkyl having from 1 to 7 carbons can be prepared from the compound of formula VIII, via the reaction scheme in Scheme 5.

10

In Scheme 5, t, n, A,  $\text{R}^9$  and  $\text{R}^1$  are as above.  $\text{R}^7$  is an alkyl group having 1 to 7 carbon atoms.

15

The compound of formula VIII is prepared in the same manner as described hereinbefore in connection with reaction of step (a) or (b) in Scheme 1.

20

The compound of formula VIII is converted to compound of formula XXVI by selective bromination of the methyl ketone moiety via reaction of step (n) by treating the compound of formula VIII with  $\text{CuBr}_2$ . Any selective bromination conditions to convert methyl ketone to 1-bromoketone can be utilized to carry out the reaction of step (n).

25

The compound of formula XXVI can be converted to compound of formula XXVIII via reaction of step (o) by treating the compound of formula XXVI with the sodium salt of compound of formula XXVII in ethanol. Any conventional conditions for this alkylation reaction can be utilized to carry out this reaction.

30

The compound of formula XXVIII is converted to compound of formula XXIX via reaction of step (p) by de-esterification employing 4 equivalents of sodium hydroxide. Initial mono de-esterification followed by slow hydrolysis of the remaining ethyl ester

was observed. Removal of solvent and incubation of the residue in acetic acid produced the compound of formula XXIX.

The compound of formula XXIX is the compound of formula I' where R<sup>1</sup> is H.

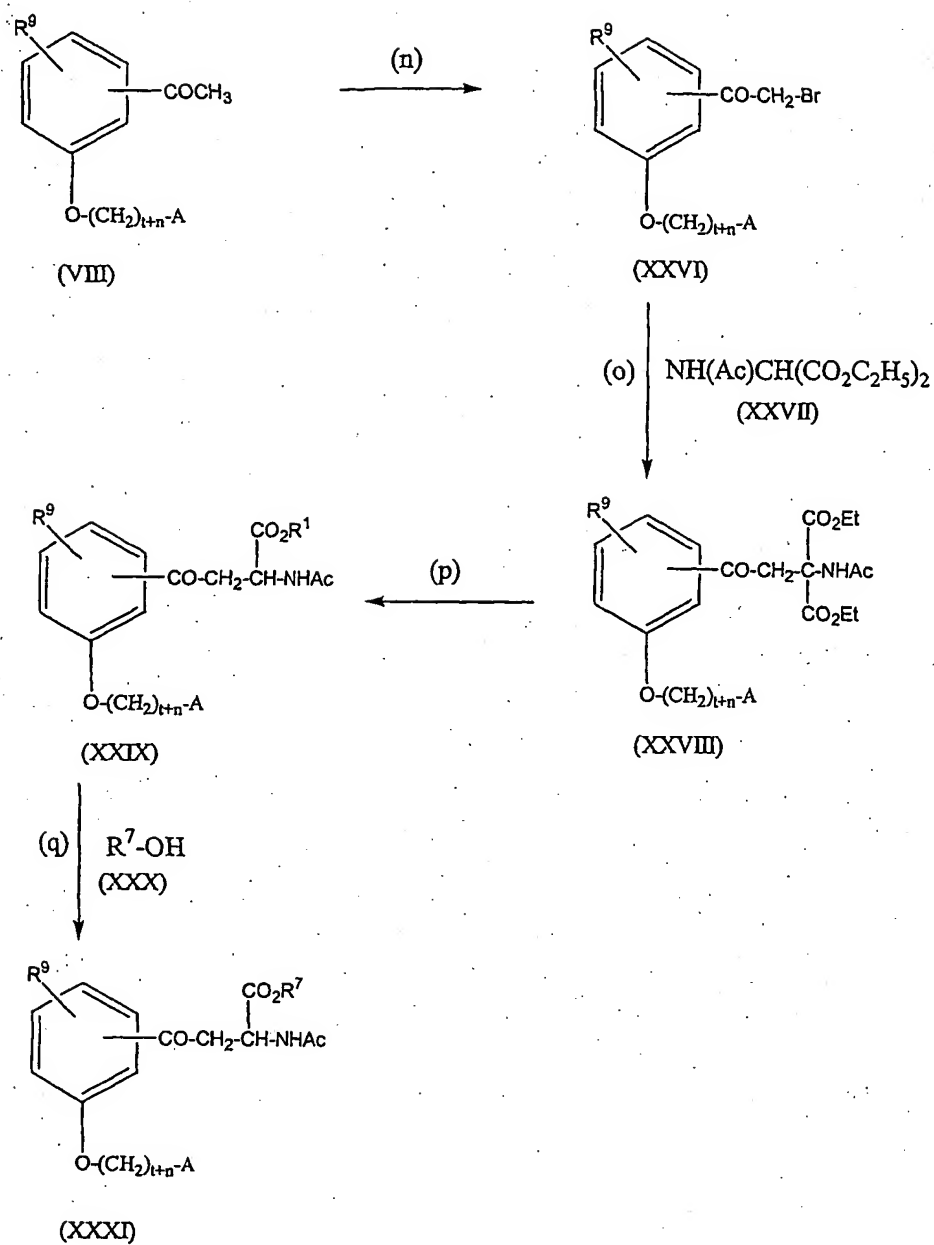
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The compound of formula XXIX can be converted to compound of formula XXXI where R<sup>7</sup> is an alkyl chain having 1 to 7 carbon atoms by esterification of carboxylic acid with compound of formula XXX using N,N-dicyclohexylcarbodiimide as dehydrating condensing agent. Any conditions conventional for this reaction can be

10 utilized to carry out the reaction of step (q).

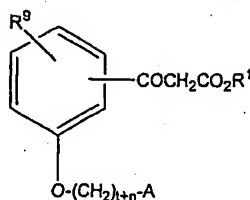
The compound of formula XXXI is the compound of formula I' where R<sup>1</sup> is an alkyl chain having 1 to 7 carbon atoms.

Scheme 5





The compound of formula I' where X is  $-\text{CH}_2-$ , q and m are 0, t is 0 or 1 and n is 1 or 2, i.e. compounds of formula:



5

wherein t, n, and A are as described above,  $R^9$  is hydrogen, halo, or alkoxy having 1 to 3 carbon atoms and  $R^1$  is ethyl can be prepared from the compound of formula LX, via the reaction scheme in Scheme 6.

- 10 In the reaction scheme of Scheme 6, A, t,  $R^9$  and n are as above, Y is a leaving group and  $Y^1$  is chloro.

15 In Scheme 6, the compound of formula LX is converted to compound of formula LXI in the same manner as described hereinbefore in connection with the reaction of steps (a) or (b) in Scheme 1.

In the step of (q'), the compound of formula LXI is hydrolyzed to produce the compound of formula LXII in the same manner as described in connection with the reaction of step (f) in Scheme 3.

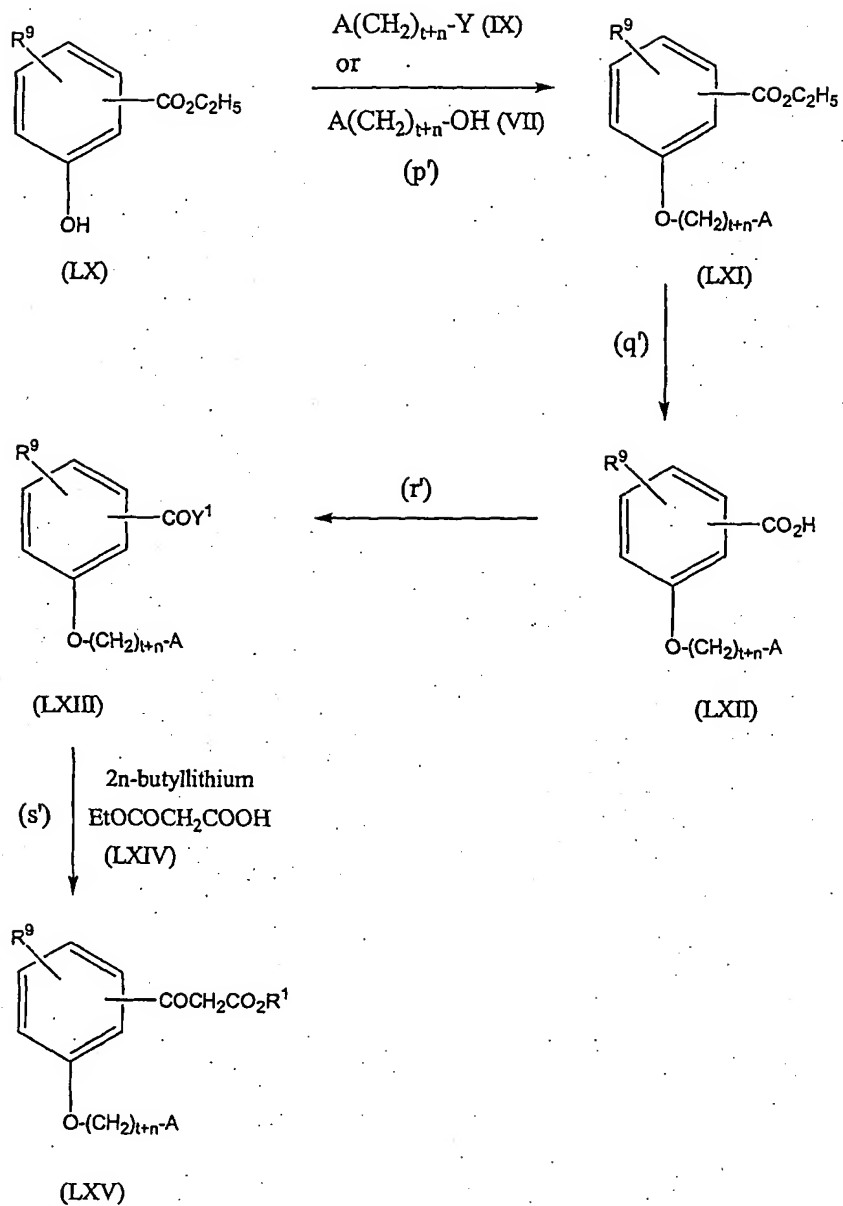
20

The compound of formula LXII is converted to compound of formula LXIII via reaction of step (r') in the same manner as described in connection with reaction of step (g) in Scheme 3.

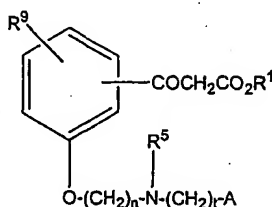
- 25 The compound of formula LXIV is first treated with 2 equivalents of n-butyllithium at low temperature and then compound of formula LXIII is added to produce compound of formula LXV (Weirenga, W.; Skulnick, H. I. J.O.C. 1979, 44, 310-311).

The compound of formula LXV is the compound of formula 1 where  $R^1$  is ethyl.  
Scheme 6

30



The compound of formula I where q is 1, R<sup>5</sup> is an alkyl group having 1 to 3 carbon atoms, where X is -CH<sub>2</sub>-, m is 0, t is 0 or 1 and n is 1 or 2, i.e. compounds of formula:



5

wherein A is as described above, R<sup>9</sup> is hydrogen, halo, or alkoxy having 1 to 3 carbon atoms and R<sup>1</sup> is ethyl can be prepared from the compound of formula LX via the reaction scheme in Scheme 7.

- 10 In the reaction scheme of Scheme 7, A, t, R<sup>9</sup> and n are as above, Y<sup>1</sup> is chloro. R<sup>5</sup> is an alkyl group having from 1 to 3 carbon atoms.

- In Scheme 7, the compound of formula LX is reacted with compound of formula XXIII (prepared in the same manner as described in Scheme 4) to produce the compound of  
15 formula LXVI via reaction of step (t'). This reaction is carried out in the same manner as described hereinbefore in the connection with reaction of step (l) in Scheme 4.

- In the step of (u'), the compound of formula LXVI is hydrolyzed to produce the compound of formula LXVII in the same manner as described in the reaction of step (f)  
20 in Scheme 3.

- The compound of formula LXVII is converted to compound of formula LXVIII via reaction of step (v') in the same manner as described in connection with the reaction of step (g) in Scheme 3.

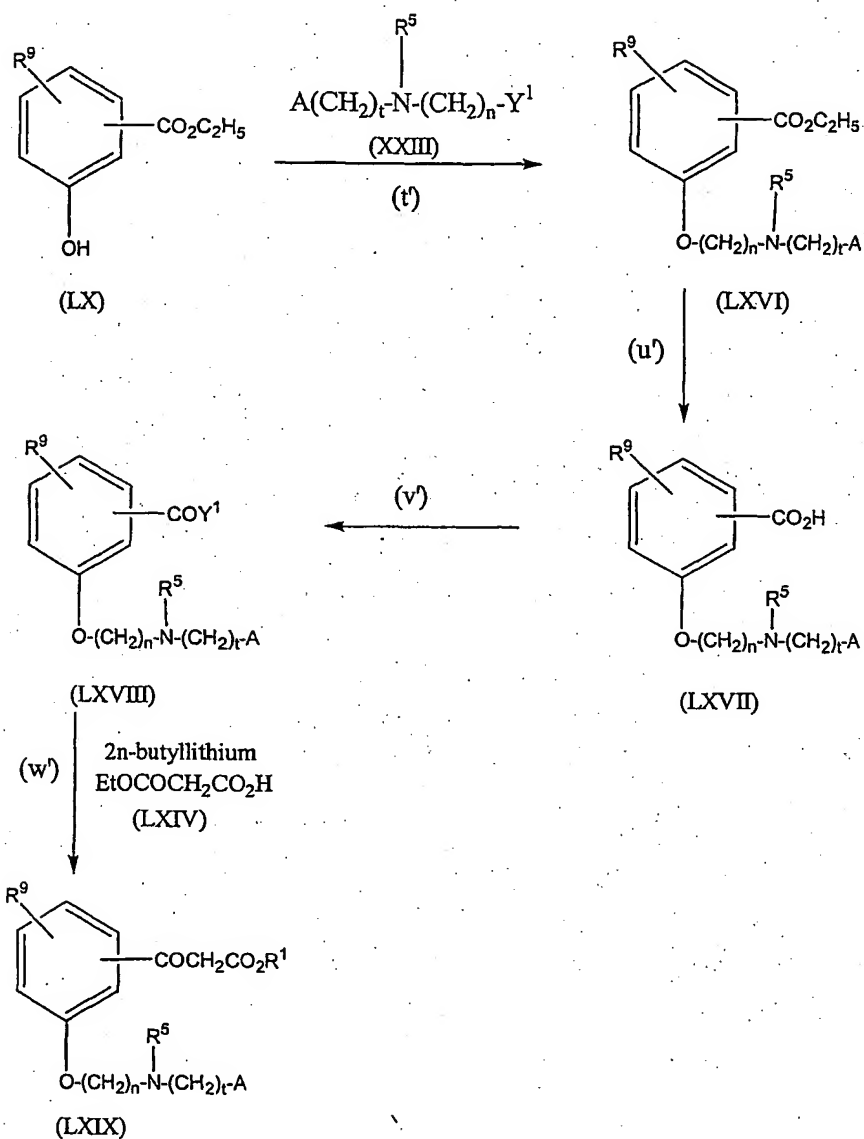
25

The compound of formula LXIV is first treated with 2 equiv of n-butyllithium at low temperature and then compound of formula LXIII is added to produce compound of formula LXV (Weirenga, W.; Skulnick, H. I. J.O.C. 1979, 44, 310-311).

The compound of formula LXIX is the compound of formula I' where R<sup>1</sup> is an alkyl group having 2 carbon atoms.

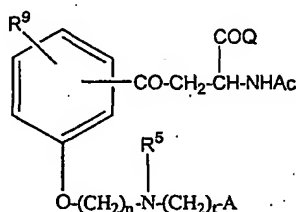
Scheme 7

5



The compound of formula I' where q is 1, R<sup>5</sup> is an alkyl group having 1 to 3 carbon atoms, R<sup>1</sup> is hydrogen or alkyl having from 1 to 7 carbons, R<sup>9</sup> is hydrogen, halo, or alkoxy having 1 to 3 carbon atoms, Q is OR<sup>1</sup> where R<sup>1</sup> is hydrogen or alkyl having from 1 to 7 carbons, X is -CH<sub>2</sub>CH(NHAc)-, m is 0, t is 0 or 1 and n is 1 or 2, i.e.

5 compounds of the formula:



wherein t, n, A and R<sup>1</sup> are as above, can be prepared from the compound of formula VI, via the reaction scheme in Scheme 8.

In Scheme 8, t, n, A, R<sup>9</sup> and R<sup>1</sup> are as above. R<sup>7</sup> is an alkyl group having 1 to 7 carbon atoms. R<sup>5</sup> is an alkyl group having 1 to 3 carbon atoms. Y<sup>1</sup> is chloro.

15 The compound of formula XXIV is prepared in the same manner as described hereinbefore in connection with reaction of step (l) in Scheme 4.

The compound of formula XXIV is converted to compound of formula LXX by selective bromination of the methyl ketone moiety via reaction of step (x') by treating the compound of formula XXIV with CuBr<sub>2</sub>. Any selective bromination conditions to convert methyl ketone to 1-bromoketone can be utilized to carry out the reaction of step (x').

25 The compound of formula LXX can be converted to the compound of formula LXXI via reaction of step (y') by treating the compound of formula LXX with the sodium salt of compound of formula XXVII in ethanol. Any conventional conditions can be utilized to carry out alkylation reaction.

30 The compound of formula LXXI is converted to the compound of formula LXXII via reaction of step (z') by de-esterification employing 4 equiv. of sodium hydroxide. This

indicated an initial mono de-esterification followed by slow hydrolysis of the remaining ethyl ester. Removal of solvent and incubation of the residue in acetic acid produced the compound of formula LXXII.

- 5 The compound of formula LXXII is the compound of formula I' where R<sup>1</sup> is H.

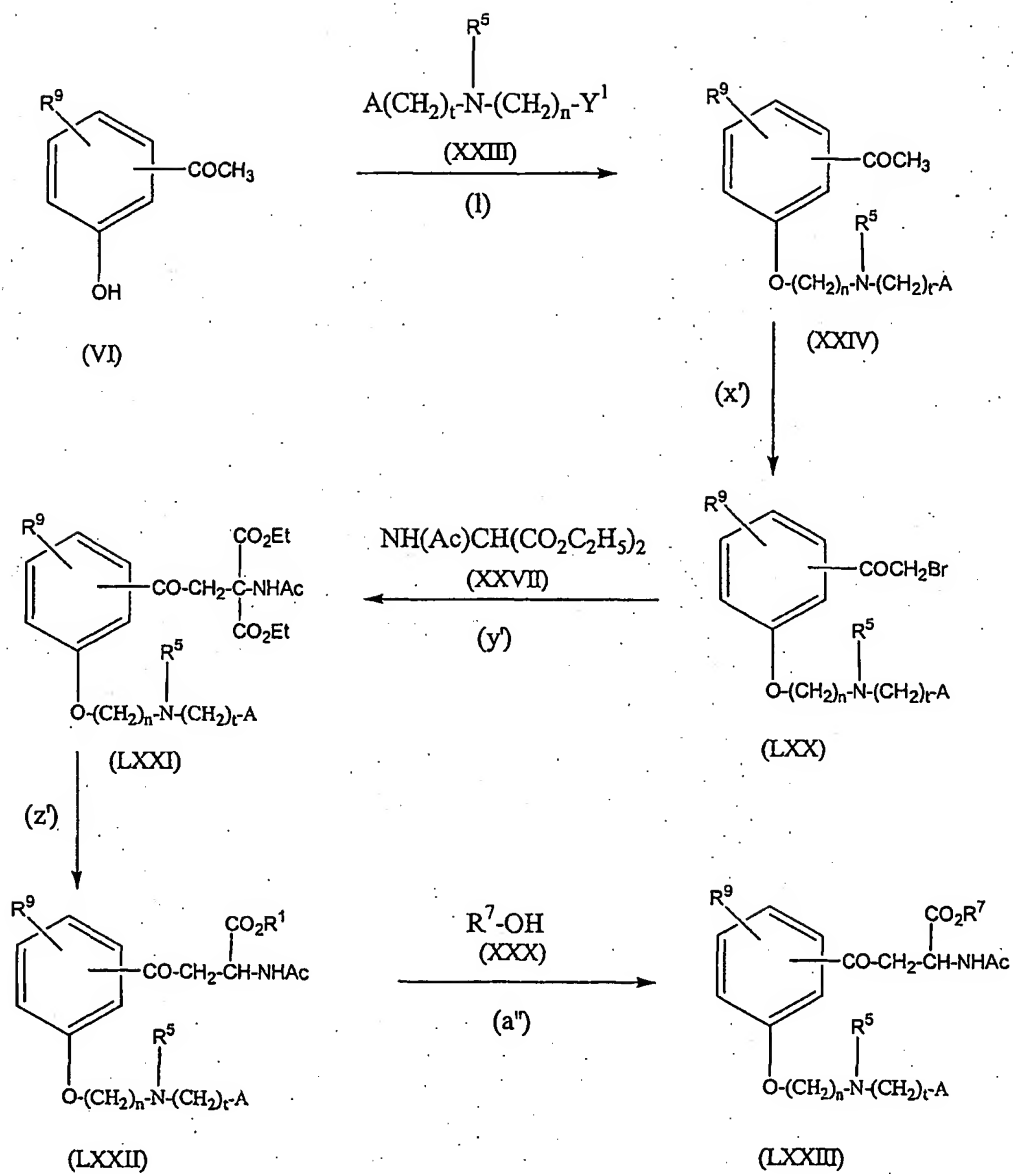
The compound of formula LXXII can be converted to compound of formula LXXIII where R<sup>7</sup> is an alkyl group having 1 to 7 carbon atoms by esterification of carboxylic acid with compound of formula XXX using N,N-dicyclohexylcarbodiimide as

- 10 dehydrating condensing agent. Any conditions conventional for this reaction can be utilized to carry out the reaction of step (a'').

The compound of formula LXXIII is the compound of formula I' where R<sup>1</sup> is an alkyl group having 1 to 7 carbon atoms.

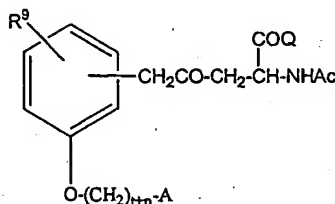
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Scheme 8



The compound of formula I' where X is  $-\text{CH}_2\text{CH}(\text{NHAc})-$ ,  $\text{R}^9$  is hydrogen, halo, or alkoxy having 1 to 3 carbon atoms, Q is  $\text{OR}^1$  where  $\text{R}^1$  is hydrogen or alkyl having from 1 to 7 carbons, m is 1, q is 0, t is 0 or 1 and n is 1 or 2, i.e. compounds of the formula:

5



wherein A is as above, and  $\text{R}^1$  is hydrogen or alkyl having from 1 to 7 carbon atoms can be prepared from the compound of formula LXXIV via the reaction scheme in Scheme 9.

10

In Scheme 9, t, n, A,  $\text{R}^9$  and  $\text{R}^1$  are as above.  $\text{R}^7$  is an alkyl group having 1 to 7 carbon atoms.  $\text{R}^5$  is an alkyl group having 1 to 3 carbon atoms.

15 The compound of formula LXXIV can be prepared according to method described in Murphy et al J.C.S. Perkin 1, 1980, 1555-1566.

The compound of formula LXXIV can be alkylated to produce compound of formula LXXV via reaction of step (b'') employing either compound of formula VII using same method as described in the connection of reaction step of (a) in Scheme 1 or compound of formula IX using potassium carbonate as the base for alkylation. The reaction is carried out in the same manner as described hereinbefore in connection with the reaction of step (l) in Scheme 4.

25 The compound of formula LXXV is then selectively brominated at  $0^\circ\text{C}$  using 30 wt% HBr in acetic acid dropwise to produce compound of formula LXXVI via reaction of step (c''). Any conventional method to convert selectively substituted acetone to 1-Bromoacetone can be utilized to carry out this reaction of step (c'').



The compound of formula LXXVI is converted to compound of formula LXXVII via reaction of step (d'') in the same manner as described hereinbefore in connection with the reaction of step (o) in Scheme 5.

- 5 The compound of formula LXXVII is converted to compound of formula LXXVIII via reaction of step (e'') by de-esterification employing 4 equiv. of sodium hydroxide. Initial mono de-esterification followed by slow hydrolysis of the remaining ethyl ester was observed. Removal of solvent and incubation of the residue in acetic acid produced the compound of formula LXXVIII.

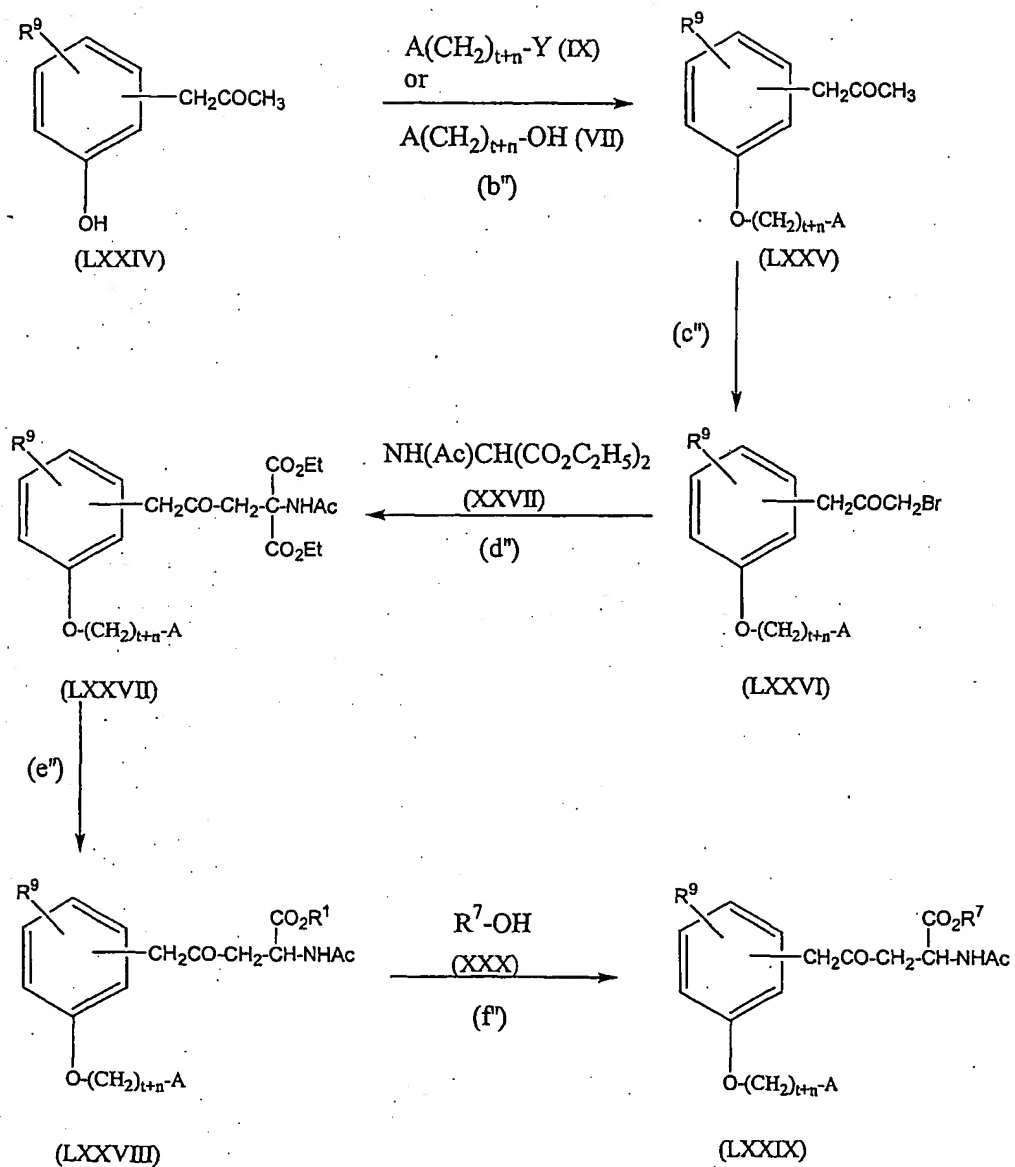
10

The compound of formula LXXVIII is the compound of formula I' where R<sup>1</sup> is H.

The compound of formula LXXVIII can be converted to compound of formula LXXIX where R<sup>7</sup> is an alkyl group having 1 to 7 carbon atoms by esterification of carboxylic  
15 acid with compound of formula XXX using N,N-dicyclohexylcarbodiimide as dehydrating condensing agent. Any conditions conventional for this reaction can be utilized to carry out the reaction of step (f'').

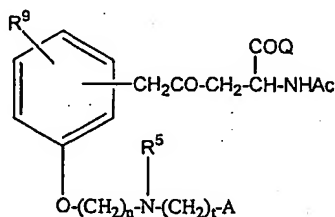
- 20 The compound of formula LXXIX is the compound of formula I' where R<sup>1</sup> is an alkyl group having 1 to 7 carbon atoms.

Scheme 9



The compound of formula I' where q is 1, R<sup>5</sup> is an alkyl group having 1 to 3 carbon atoms, X is -CH<sub>2</sub>CH(NHAc)-, m is 1, t is 0 or 1 and n is 1 or 2, R<sup>9</sup> is hydrogen, halo, or alkoxy having 1 to 3 carbon atoms, Q is OR<sup>1</sup> where R<sup>1</sup> is hydrogen or alkyl having from 1 to 7 carbons, i.e. compounds of the formula:

5



wherein A is as above, and R<sup>1</sup> is hydrogen or alkyl having from 1 to 7 carbon atoms can be prepared from the compound of the formula LXXIV via the reaction scheme in Scheme 10.

10

In Scheme 10, t, n, A, R<sup>9</sup> and R<sup>1</sup> are as above. R<sup>7</sup> is an alkyl group having 1 to 7 carbon atoms. R<sup>5</sup> is an alkyl group having 1 to 3 carbon atoms. Y<sup>1</sup> is chloro.

The compound of formula LXXIV can be prepared according to method described in Murphy et. al. J.C.S. Perkin 1, 1980, 1555-1566.

15

In Scheme 10, the compound of formula LXXIV is reacted with compound of formula XXIII (prepared in the same manner as described in Scheme 4) to produce the compound of formula LXXX via reaction of step (g''). This reaction is carried out in the same manner as described hereinbefore in connection with the reaction of step (l) in Scheme 4.

20

The compound of formula LXXX is then selectively brominated at 0°C using 30 wt% HBr in acetic acid dropwise to produce compound of formula LXXXI via reaction of step (h''). Any conventional method to convert substituted acetone to 1-Bromoacetone can be utilized to carry out the reaction of step (h'').

25

The compound of formula LXXXI is converted to the compound of formula LXXXII via reaction of step (i'') in the same manner as described hereinbefore in connection with the reaction of step (o) in Scheme 5.

30

The compound of formula LXXXII is converted to compound of formula LXXXIII via reaction of step (j'') in the same manner as described in reaction of step (p) in Scheme 5.

5

The compound of formula LXXXIII is the compound of formula I' where  $R^1$  is H.

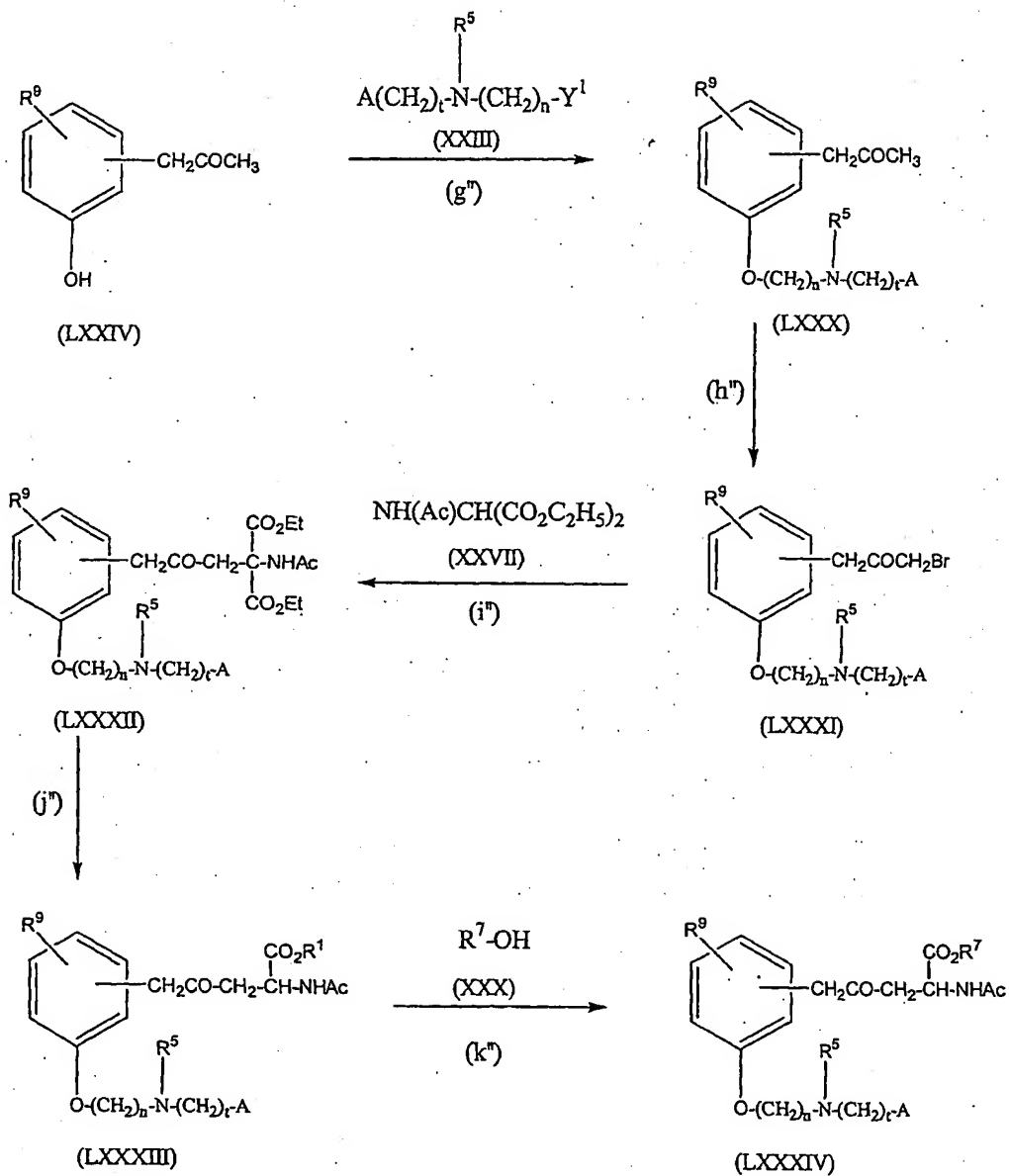
The compound of formula LXXXIII can be converted to compound of formula LXXXIV where  $R^7$  is an alkyl chain having 1 to 7 carbon atoms by esterification of carboxylic acid with compound of formula XXX using N,N-dicyclohexylcarbodiimide as dehydrating condensing agent. Any conditions conventional for this reaction can be utilized to carry out the reaction of step (k'').

10

The compound of formula LXXXIV is the compound of formula I' where  $R^1$  is an alkyl group having 1 to 7 carbon atoms.

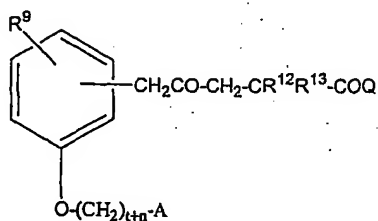
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Scheme 10



The compound of formula I' where X is  $-\text{CH}_2\text{CR}^{12}\text{R}^{13}-$ ,  $\text{R}^9$  is hydrogen, halo, or alkoxy having 1 to 3 carbon atoms, Q is  $\text{OR}^1$  where  $\text{R}^1$  is hydrogen or alkyl having from 1 to 7 carbons, q is 0, m is 1, t is 0 or 1 and n is 1 or 2, i.e. compounds of formula:

5



wherein A is as described above,  $\text{R}^1$  is hydrogen or alkyl having from 1 to 7 carbon atoms, and  $\text{R}^{12}$  and  $\text{R}^{13}$  is independently hydrogen or methyl can be prepared from the compound of the formula LXXIV, via the reaction scheme in Scheme 11.

In the reaction scheme of Scheme 11, A, t,  $\text{R}^9$ ,  $\text{R}^{12}$ ,  $\text{R}^{13}$  and n are as above.  $\text{R}^6$  is an alkyl group containing from 1 to 7 carbon atoms, and Y is a leaving group.

The compound formula LXXV is produced from compound of formula LXXIV in the same manner as described hereinbefore in connection with the reaction of step (b'') in Scheme 9.

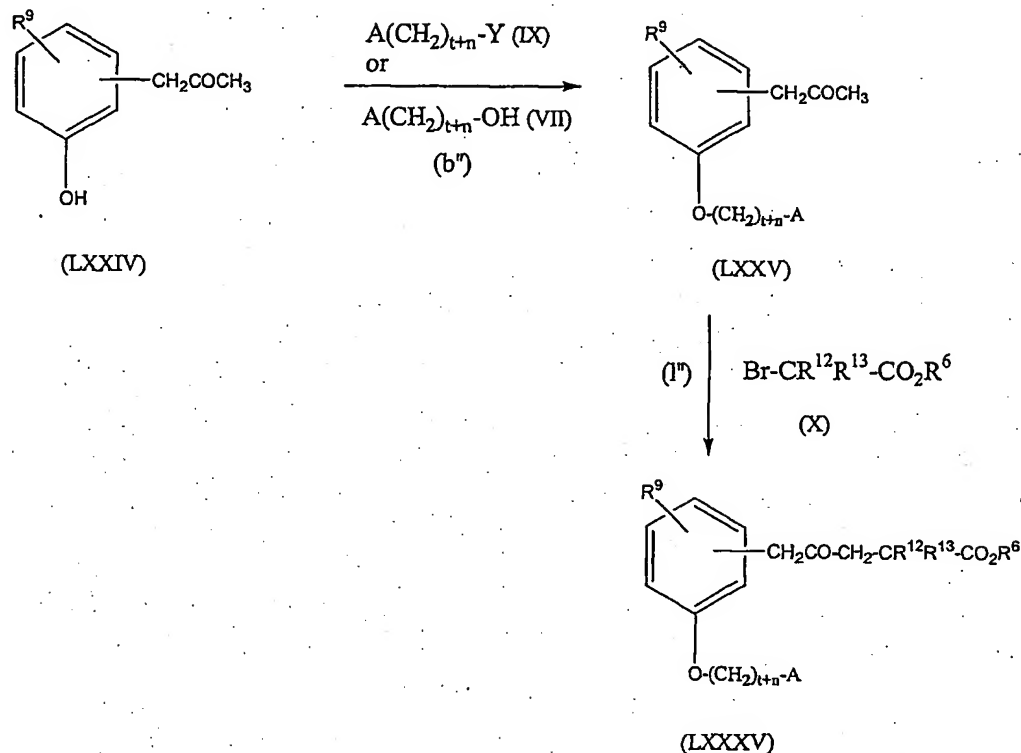
The compound of formula LXXV is converted to compound of formula LXXXV via reaction of step (1'') by selectively alkylating the compound of formula LXXV with the compound of formula X. This reaction is carried out utilizing a conventional base which converts substituted ketone to gamma-keto ester. In carrying out this reaction it is generally preferred to utilize lithium diisopropylamide as base. Alkylation will occur at the less hindered methyl group. Generally this reaction is carried out in an inert solvent such as tetrahydrofuran or 1,2-dimethoxyethane at  $-78^\circ\text{C}$ .

The compound of formula LXXXV is the compound of formula I' where  $\text{R}^1$  is an alkyl group containing from 1 to 7 carbon atoms. The compound of formula LXXXV can be converted to the free acid i.e. the compound of formula I' where  $\text{R}^1$  is H by ester

hydrolysis. Any conventional method of ester hydrolysis will produce the compound of formula I' where R<sup>1</sup> is H.

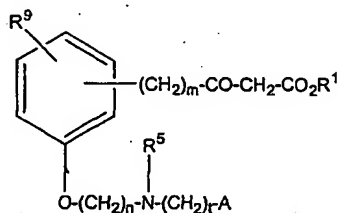
Scheme 11

5



The compound of formula I' where q is 1, R<sup>5</sup> is an alkyl group having 1 to 3 carbon atoms where X is -CH<sub>2</sub>-, m is 1, t is 0 or 1 and n is 1 or 2, i.e. compounds of the

10 formula:



wherein A is as above, R<sup>9</sup> is hydrogen, halo, or alkoxy having 1 to 3 carbon atoms and R<sup>1</sup> is ethyl can be prepared from the compound formula XIII wherein, m is as above via the reaction scheme in Scheme 12.

15

In Scheme 12, A is as above. Y<sup>1</sup> is chloro.

The compound of formula XIII (prepared in the same manner as described hereinbefore in connection with the reaction of step (d) in Scheme 3) can be converted to compound  
5 of formula LXXXVI via reaction of step (m'') in the same manner as described in the connection with reaction of step (l) in Scheme 4 hereinbefore.

In the step of (n''), the compound of formula LXXXVI is hydrolyzed to produce the compound of formula LXXXVII. Any conventional method of basic hydrolysis to  
10 hydrolyze ester can be utilized to carry out this reaction.

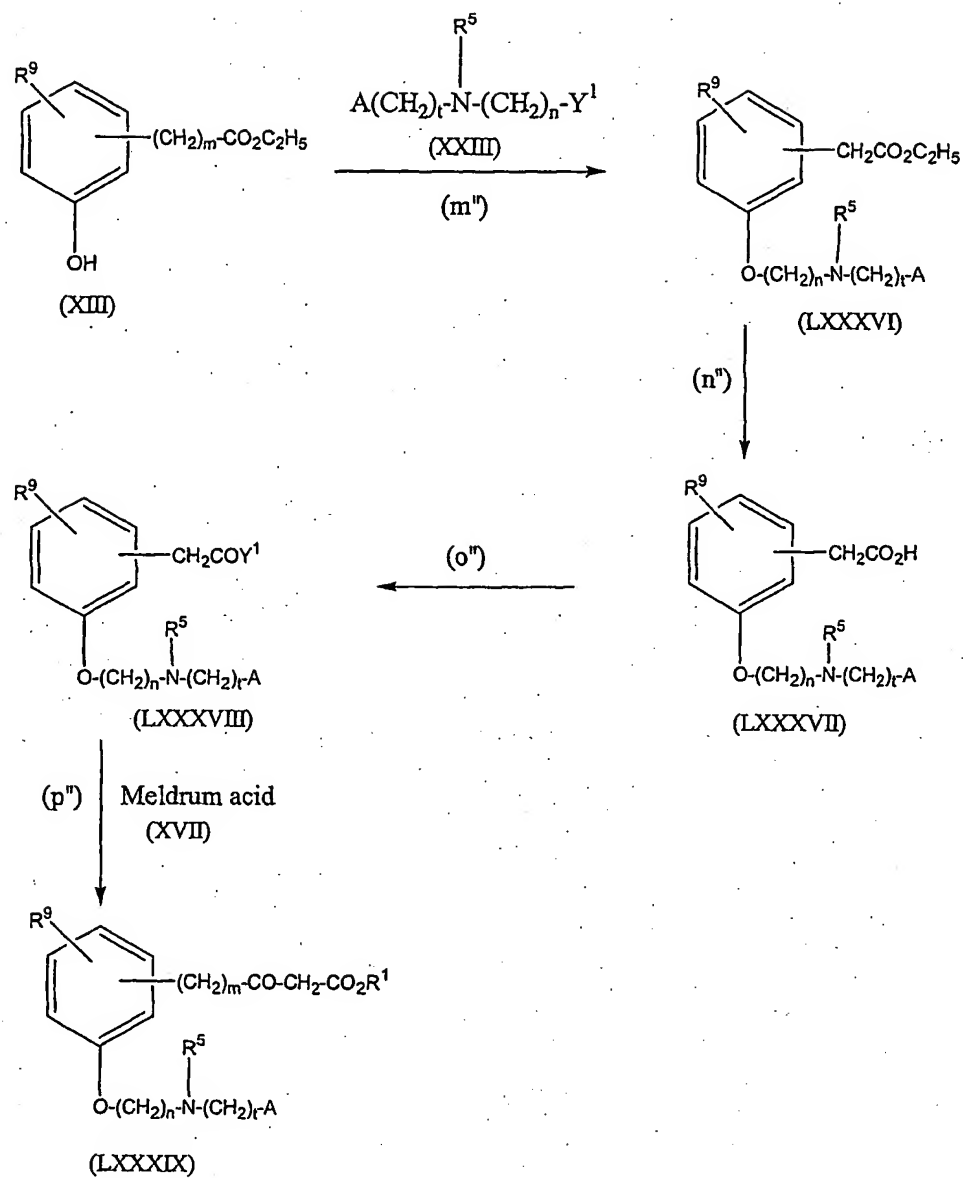
The compound of formula LXXXVII is converted to acid chloride of formula LXXXVIII via reaction of step (o'') by reaction with thionyl chloride. Any of the conventional method of converting acid to acid halide can be utilized to carry out the  
15 reaction.

The compound of formula XVII is reacted with the compound of formula LXXXVIII to produce the compound of formula LXXXIX via reaction of step (p''). Any conventional base can be used to carry out this reaction with the preferred base being pyridine. Any conventional conditions to carry out the reaction of step (p'') can be  
20 utilized.

The compound of formula LXXXIX is the compound of formula I where R<sup>1</sup> is ethyl.

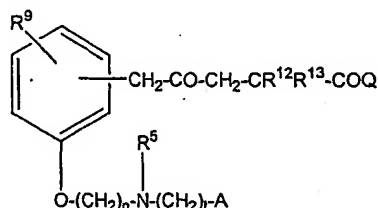


Scheme 12



The compound of formula I' where q is 1, R<sup>5</sup> is an alkyl group having 1 to 3 carbon atoms, where X is -CH<sub>2</sub>CR<sup>12</sup>R<sup>13</sup>-, R<sup>9</sup> is hydrogen, halo, or alkoxy having 1 to 3 carbon atoms, Q is OR<sup>1</sup> where R<sup>1</sup> is hydrogen or alkyl having from 1 to 7 carbons, m is 1, t is 0 or 1 and n is 1 or 2, i.e. compounds of formula:

5



wherein A is as described above, R<sup>1</sup> is hydrogen or alkyl having from 1 to 7 carbon atoms, and R<sup>12</sup> and R<sup>13</sup> is independently hydrogen or methyl can be prepared from the compound of the formula LXXIV, via the reaction scheme in Scheme 13.

In the reaction scheme of Scheme 13, R<sup>9</sup>, R<sup>12</sup>, R<sup>13</sup>, R<sup>5</sup>, A, t, and n are as above. R<sup>6</sup> is an alkyl group containing from 1 to 7 carbon atoms.

15

The compound formula LXXX is produced from compound of formula LXXIV in the same manner as described hereinbefore in connection with the reaction of step (g'') in Scheme 10.

The compound of formula LXXX is converted to compound of formula XC via reaction of step (q'') by alkylating the compound of formula LXXX with the compound of formula X. This reaction is carried out utilizing a conventional base which converts ketone to 3-keto ester. In carrying out this reaction it is generally preferred to utilize lithium diisopropylamide as base. Alkylation will occur at the less hindered methyl group. Generally this reaction is carried out in an inert solvent such as tetrahydrofuran or 1,2-dimethoxyethane at -78°C.

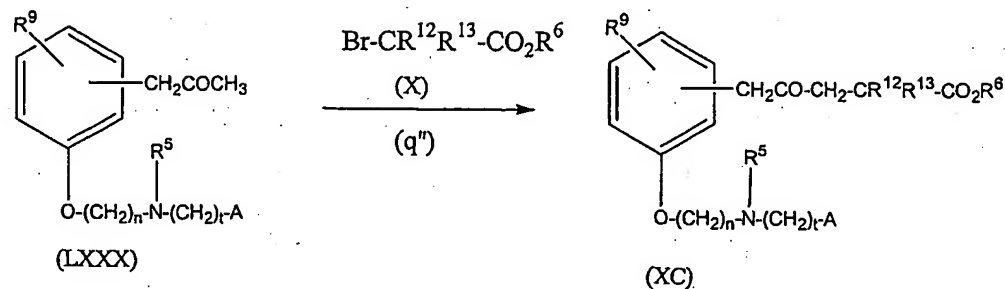
The compound of formula XC is the compound of formula I' where R<sup>1</sup> is an alkyl group containing from 1 to 7 carbon atoms. The compound of formula XC can be converted to the free acid i.e. the compound of formula I' where R<sup>1</sup> is H by ester

30

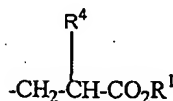
hydrolysis. Any conventional method of ester hydrolysis will produce the compound of formula I' where  $R^1$  is H.

Scheme 13

5

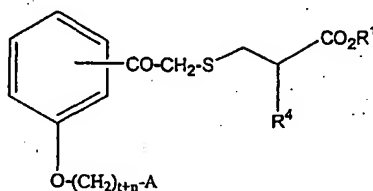


10 The compound of formula II where Z is



m is 0, r is 1, q is 0, t is 0 or 1 and n is 1 or 2,  $R^4$  is  $-NHCO_2C(CH_3)_3$ ,  $-NHCH_3$ , or

15  $-NHCH_2CH_3$ , i.e. the compounds of formula:



wherein A and  $R^1$  are as above, can be prepared from the compound of formula XXVI

20 via reaction scheme in Scheme 14.

In Scheme 14, t, n, A and  $R^1$  are as above.  $R^7$  is an alkyl group having 1 to 7 carbon atoms.  $R^8$  is an alkyl group containing from 1 to 2 carbon atoms.  $Y^1$  is halo preferably bromo.

In Scheme 14, the compound of formula XXVI (prepared in the same manner as described hereinbefore in connection with reaction of step (n) in Scheme 5) is reacted with the compound of formula XXXII in the presence of a base to produce the compound of formula XXXIII via reaction of step (r). In carrying out this reaction it is  
5 generally preferred to utilize triethylamine as base. Any conventional method of reacting Boc-cys-OEt with halide can be utilized to carry out this reaction.

The compound of formula XXXIII is compound of formula II where  $R^4$  is  $-\text{NHCO}_2\text{C}(\text{CH}_3)_3$  and  $R^1$  is ethyl.

10

The compound of formula XXXIII can be converted to the free acid i.e. the compound of formula II where  $R^1$  is H by ester hydrolysis. Any conventional method of ester hydrolysis will produce the compound of formula II where  $R^1$  is H and  $R^4$  is  $-\text{NHCO}_2\text{C}(\text{CH}_3)_3$ .

15

The compound of formula XXXIII is converted to compound of formula XXXV first via reaction of step (s) by deprotecting t-butoxy group using trifluoroacetic acid and replacing by lower alkyl having 1 to 2 carbon atoms via reaction of step (t). Any conventional method to condense amine with alkyl halide can be used to carry out this reaction.

20

The compound of formula XXXV is compound of formula II where  $R^4$  is an amine having 1 to 2 carbon atoms and  $R^1$  is an alkyl group having 2 carbon atoms.

The compound of formula XXXV can be converted to the free acid i.e. the compound of formula XXXVI where  $R^1$  is H by basic hydrolysis via reaction of step (u). The

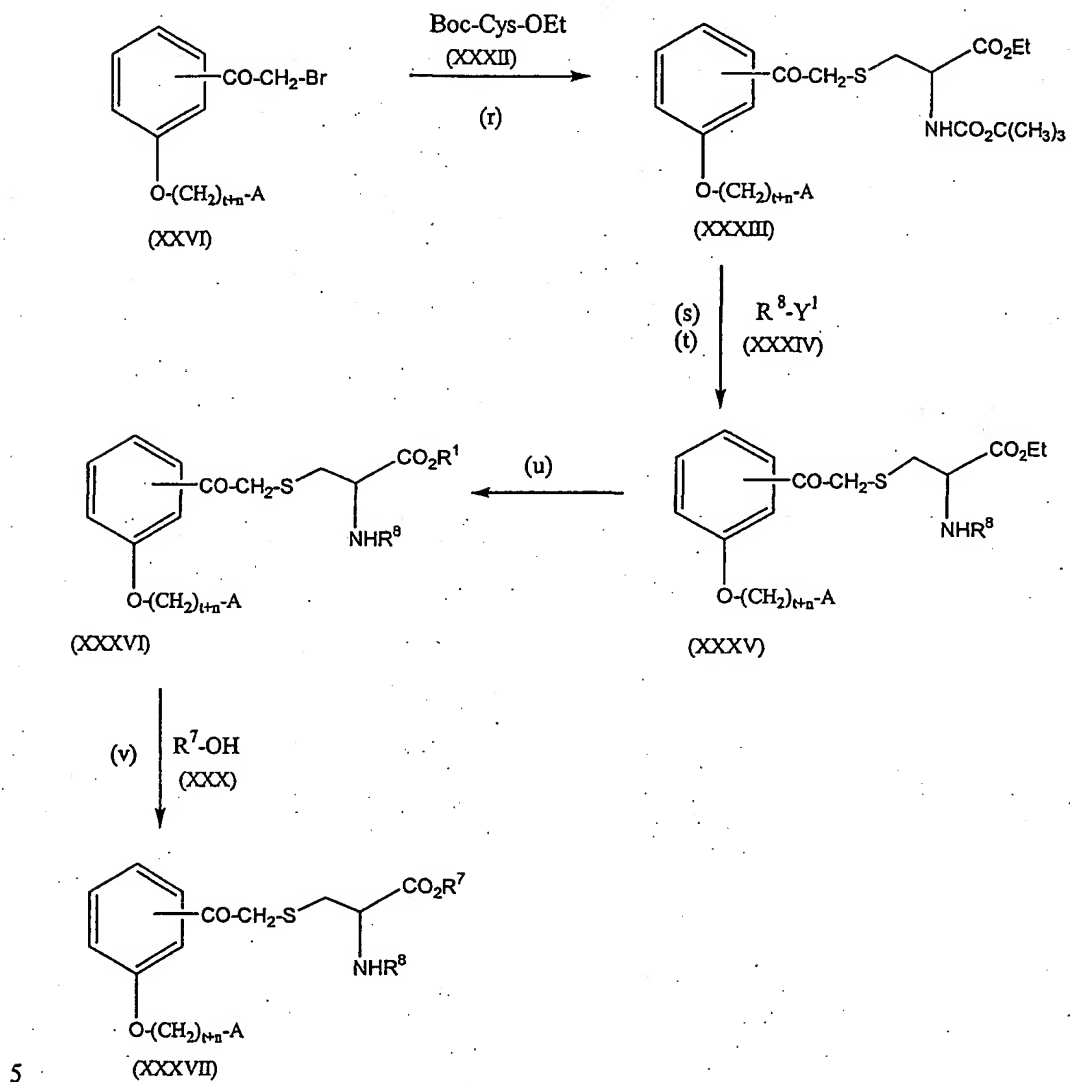
25

compound of formula XXXVI is compound of formula II where  $R^4$  is  $-\text{NHCH}_3$  or  $-\text{NHCH}_2\text{CH}_3$  and  $R^1$  is H.

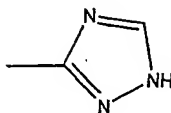
The compound of formula XXXVI can be converted to compound of formula XXXVII where  $R^7$  is an alkyl group having 1 to 7 carbon atoms by esterification of carboxylic  
30 acid with compound of formula XXX using N,N-dicyclohexylcarbodiimide as dehydrating condensing agent. Any conditions conventional for this reaction can be utilized to carry out the reaction of step (v).

The compound of formula XXXVII is compound of formula II where  $R^1$  is an alkyl having 1 to 7 carbon atoms and  $R^4$  is  $-NHCH_3$  or  $-NHCH_2CH_3$ .

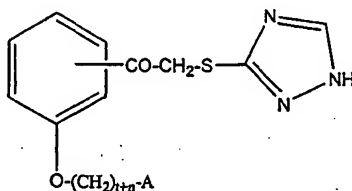
Scheme 14



The compound of formula II where Z is



5 m and q are 0, r is 1, t is 0 or 1, n is 1 or 2, i.e. compounds of the formula:

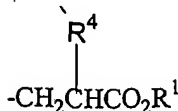


A is as above, can be prepared from the compound of formula VIII, wherein t, n and A  
10 are as above, via the reaction scheme in Scheme 15.

In Scheme 15, the compound of formula VIII (prepared in the same manner as  
described hereinbefore in connection with reaction of step (a) or (b) in Scheme 1) is  
converted to compound of formula XXVI in the same manner as described in reaction  
15 of step (n) in Scheme 5.

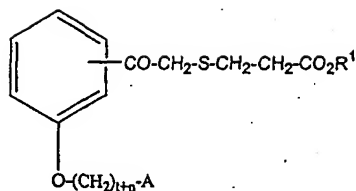
The compound of formula XXVI is reacted with compound of formula XXXVIII in the  
presence of base preferred base being triethylamine to produce the compound of  
formula XXXIX. Any conventional method to react thiol with halide can be utilized to  
20 carry out the reaction of step (w).

The compound of formula II where Z is



25

m is 0, r is 1, t is 0 or 1 and n is 1 or 2,  $R^4$  is H, i.e. compounds of formula:



wherein t, n, A and  $\text{R}^1$  are as above, can be prepared from the compound of formula VIII via the reaction scheme in Scheme 15.

5

In the reaction scheme of Scheme 15, t, n, A and  $\text{R}^1$  are as above.  $\text{R}^6$  is an alkyl group having 1 to 7 carbon atoms.

The compound of formula VIII is prepared in same manner as described hereinbefore in connection with the reaction of step (a) or (b) in Scheme 1.

10

The compound of formula XXVI is prepared from compound of formula VIII in the same manner as described hereinbefore in connection with the reaction of step (n) in Scheme 5.

15

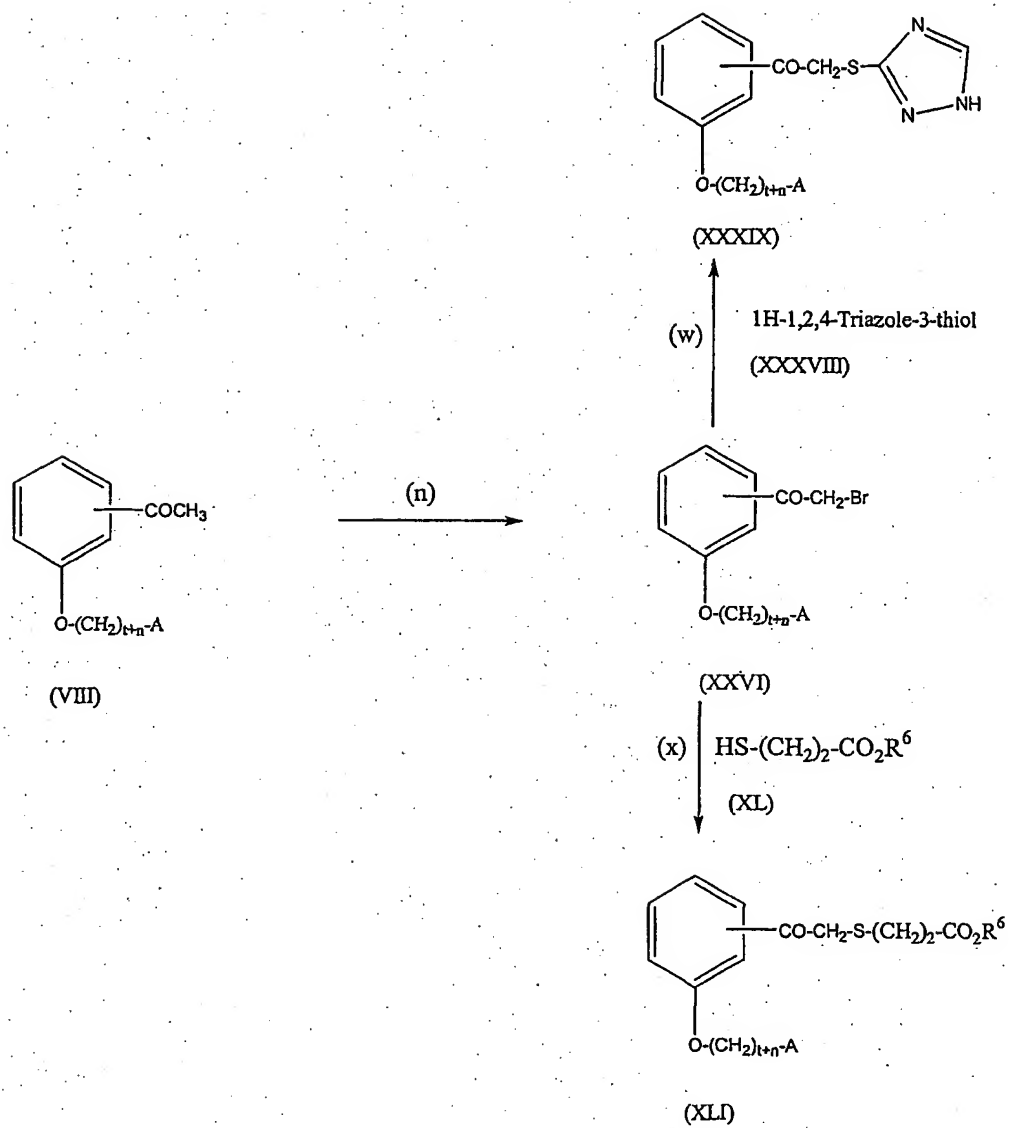
The compound of formula XXVI is reacted with compound of formula XL in the presence of base preferred base being triethylamine to produce compound of formula XLI. Any conventional method to react thiol with 1-bromoketone can be utilized to carry out the reaction of step (x).

20

The compound of formula XLI is the compound of formula II where  $\text{R}^1$  is an alkyl group containing from 1 to 7 carbon atoms. The compound of formula XLI can be converted to the free acid i.e. the compound of formula II where  $\text{R}^1$  is H by ester hydrolysis. Any conventional method of ester hydrolysis will produce the compound of formula II where  $\text{R}^1$  is H.

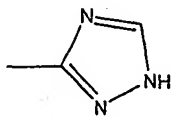
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Scheme 15

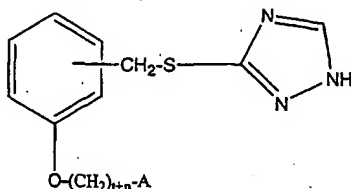




The compound of formula II where Z is



5 r is 0, m is 1, t is 0 or 1 and n is 1 or 2, i.e. compounds of formula:



wherein n, t and A are as above, can be prepared from the compound of formula XLII via the reaction scheme in Scheme 16.

10

In Scheme 16, t, n, and A are as above. Y is a leaving group such as halide, mesyloxy or tosyloxy. Y<sup>1</sup> is halo preferably bromo.

In Scheme 16, the compound of formula XLII is converted to compound of formula

15 XLIII via the reaction of step (y) by selective displacement of hydroxyl group of primary alcohol by halogen. Any conventional halogenating agent can be utilized to carry out this reaction with the preferred halogenating agent being phosphorous tribromide. This reaction is carried out in low temperature. Any conditions conventional for this method can be utilized to carry out the reaction of step (y). The  
20 compound of formula XLIII was used immediately without further purification.

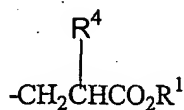
The compound of formula XLIII is reacted with compound of formula XXXVIII in the presence of base to produce the compound of formula XLIV. Any conventional method of condensing thiol with halide can be utilized to carry out the reaction of step (z). Any  
25 conventional base can be utilized to carry out this reaction with the preferred base being triethylamine.

The compound of formula XLIV is converted to the compound of formula XLV by reaction with compound of formula VII via the reaction of step (a'). This reaction is

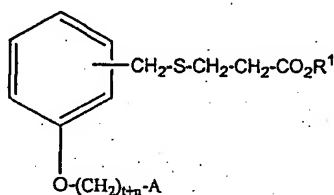
carried out in the same manner as described hereinbefore in connection with reaction of step (a) in Scheme 1.

The compound of formula II where Z is

5



r is 0, m is 1, t is 0 or 1 and n is 1 or 2,  $\text{R}^4$  is H, i.e. the compounds of formula:



10

wherein A and  $\text{R}^1$  are as above, can be prepared from the compound of formula XLII via the reaction scheme in Scheme 16.

In Scheme 16, t, n, and A are as above. Y is a leaving group such as halide, mesyloxy or tosyloxy.  $\text{Y}^1$  is halo preferably bromo.  $\text{R}^6$  is an alkyl group having 1 to 7 carbon atoms.

15

The compound of formula XLII is converted to compound of formula XLIII in the same manner as described hereinbefore in connection with the reaction of step (y).

20

The compound of formula XLIII is reacted with compound of formula XL via reaction of step (b') as described in connection with the reaction of step (x) in Scheme 15.

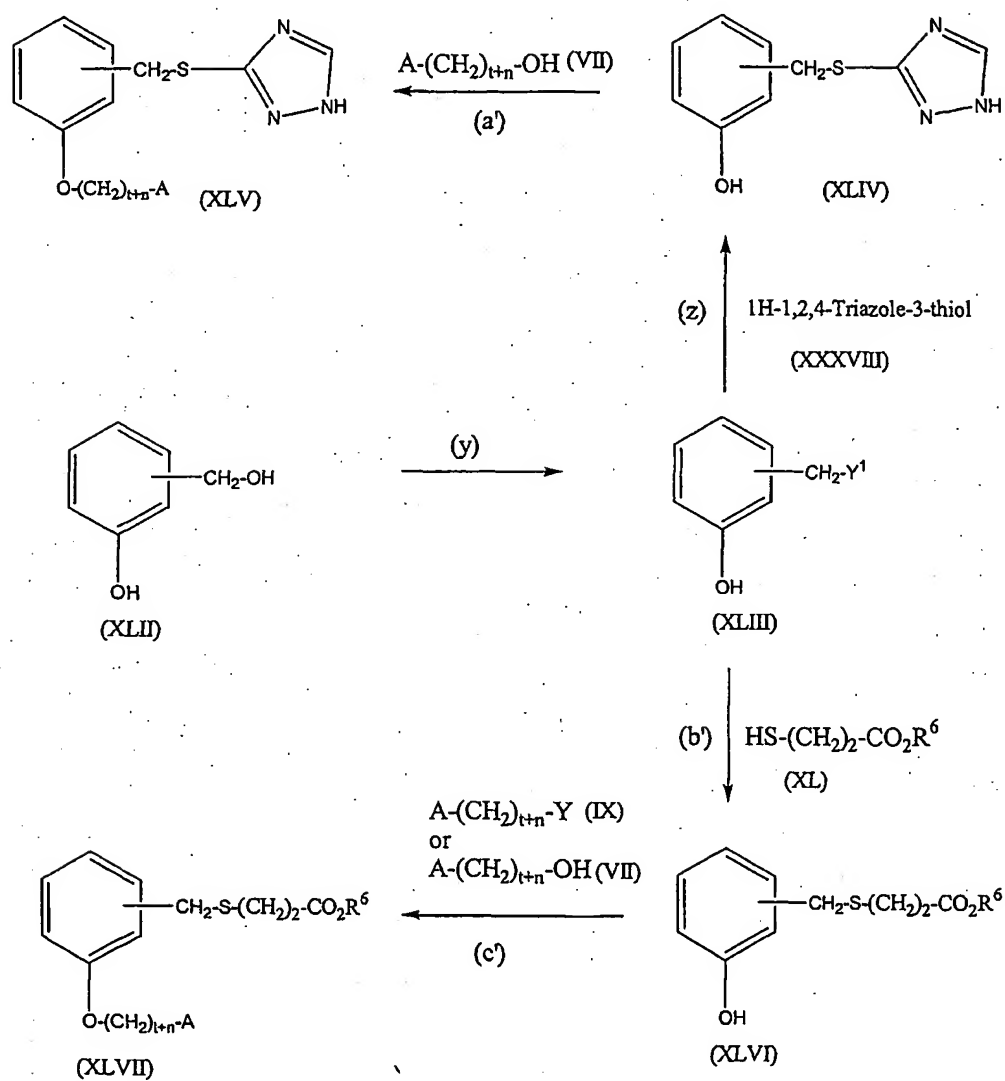
The compound of formula XLVI is converted to compound of formula XLVII via reaction of step (c'). This reaction is carried out in the same manner as described in the reaction of step (a) or (b) in Scheme 1.

25

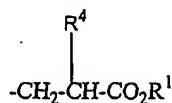
The compound of formula XLVII is the compound of formula II where  $\text{R}^1$  is an alkyl group containing from 1 to 7 carbon atoms. The compound of formula XLVII can be

converted to the free acid i.e. the compound of formula II where  $R^1$  is H by ester hydrolysis. Any conventional method of ester hydrolysis will produce the compound of formula II where  $R^1$  is H.

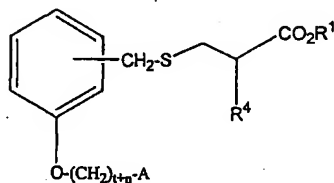
## 5 Scheme 16



The compound of formula II where Z is



5    r is 0, m is 1, t is 0 or 1 and n is 1 or 2, i.e. compounds of formula:



wherein t, n, A and  $\text{R}^1$  are as above,  $\text{R}^4$  is  $-\text{NHCO}_2\text{C}(\text{CH}_3)_3$ ,  $-\text{NHCH}_3$ ,

10     $-\text{NHCH}_2\text{CH}_3$ , can be prepared from the compound of formula XLIII via reaction scheme in Scheme 17.

In Scheme 17, t, n, A and  $\text{R}^1$  are as above. Y is a leaving group such as halide, mesyloxy or tosyloxy.  $\text{R}^7$  is an alkyl group having 1 to 7 carbon atoms and  $\text{R}^8$  is an  
15    alkyl group containing from 1 to 2 carbon atoms.  $\text{Y}^1$  is halo preferably bromo.

In Scheme 17, the compound of formula XLIII (prepared in the same manner as described hereinbefore in reaction of step (y) in Scheme 16) is reacted with the compound of formula XXXII in the presence of a base to produce the compound of  
20    formula XLVIII via reaction of step (d'). In carrying out this reaction it is generally preferred to utilize triethylamine as base. Any conventional method of reacting Boc-cyst-OEt with halide can be utilized to carry out this reaction.

The compound of formula XLIX is produced by reacting compound of formula XLVIII  
25    with compound of formula VII or IX. This reaction is carried out in the same manner as described in the reaction of step (a) or (b) in Scheme 1.

The compound of formula XLIX is compound of formula II where  $\text{R}^4$  is  $-\text{NHCO}_2\text{C}(\text{CH}_3)_3$  and  $\text{R}^1$  is an alkyl group having 2 carbon atoms.

The compound of formula XLIX can be converted to the free acid i.e. the compound of formula II where  $R^1$  is H by ester hydrolysis. Any conventional method of ester hydrolysis will produce the compound of formula II where  $R^1$  is H and  $R^4$  is  $-NHCO_2C(CH_3)_3$ .

5

The compound of formula XLIX is converted to compound of formula L first via reaction of step (f') by deprotecting t-butoxy group using trifluoroacetic acid and replacing by lower alkyl containing from 1 to 2 carbon atoms via reaction of step (g'). Any conventional method to condense amine with alkyl halide can be used to carry out this reaction.

10

The compound of formula L is compound of formula II where  $R^4$  is an amine having 1 to 2 carbon atoms and  $R^1$  is an alkyl group having 2 carbon atoms.

15 The compound of formula L can be converted to the free acid i.e. the compound of formula LI where  $R^1$  is H by basic hydrolysis via reaction of step (h').

The compound of formula LI is compound of formula II where  $R^4$  is  $-NHCH_3$  or  $-NHCH_2CH_3$  and  $R^1$  is H. Any conventional method of ester hydrolysis will produce the compound of formula II where  $R^1$  is H.

20

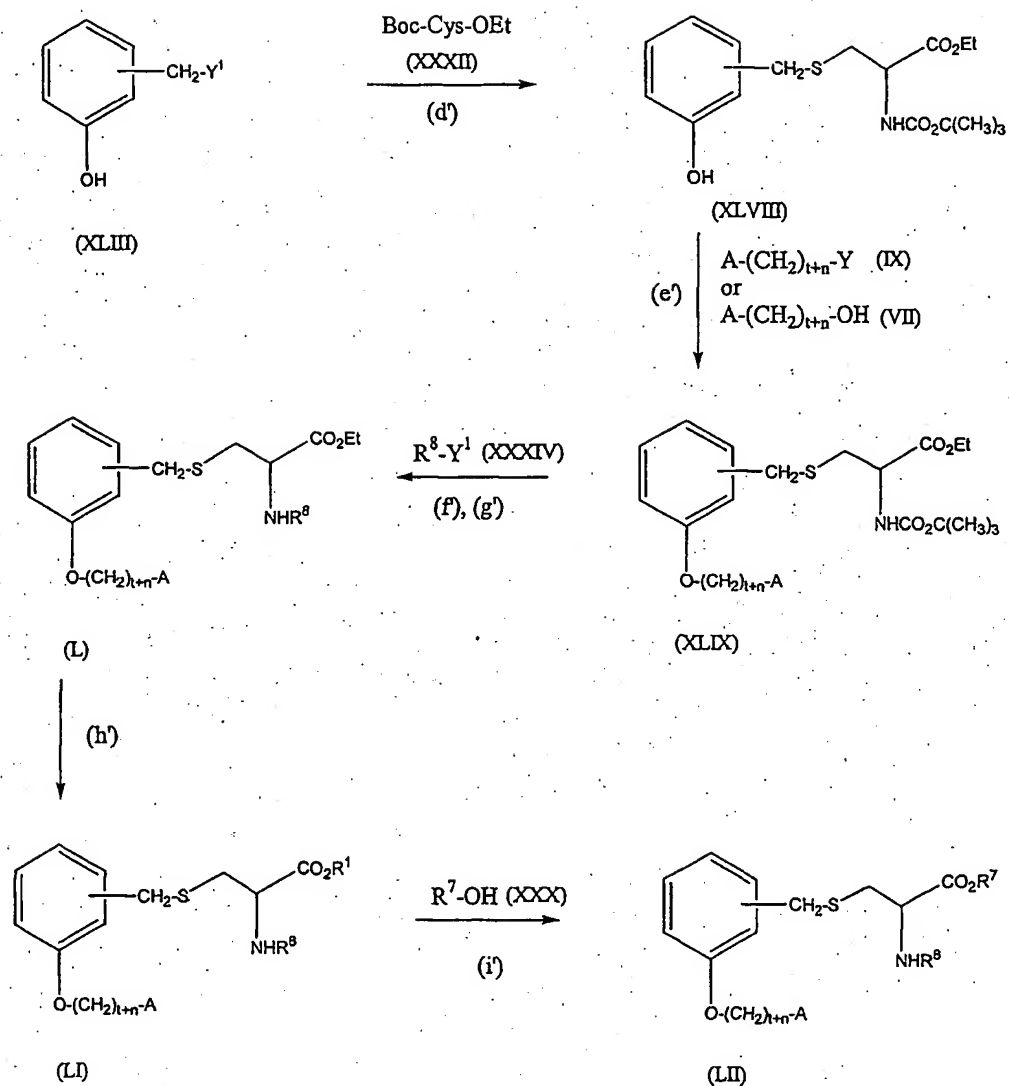
The compound of formula LI can be converted to compound of formula LII where  $R^7$  is an alkyl group having 1 to 7 carbon atoms by esterification of carboxylic acid with compound of formula XXX using N,N-dicyclohexylcarbodiimide as dehydrating condensing agent. Any conditions conventional for this reaction can be utilized to carry out the reaction of step (i').

25

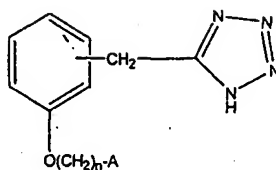
The compound of formula LII is compound of formula II where  $R^1$  is an alkyl group having 1 to 7 carbon atoms and  $R^4$  is  $-NHCH_3$  or  $-NHCH_2CH_3$ .

30

Scheme 17



## 5 The compound of formula III

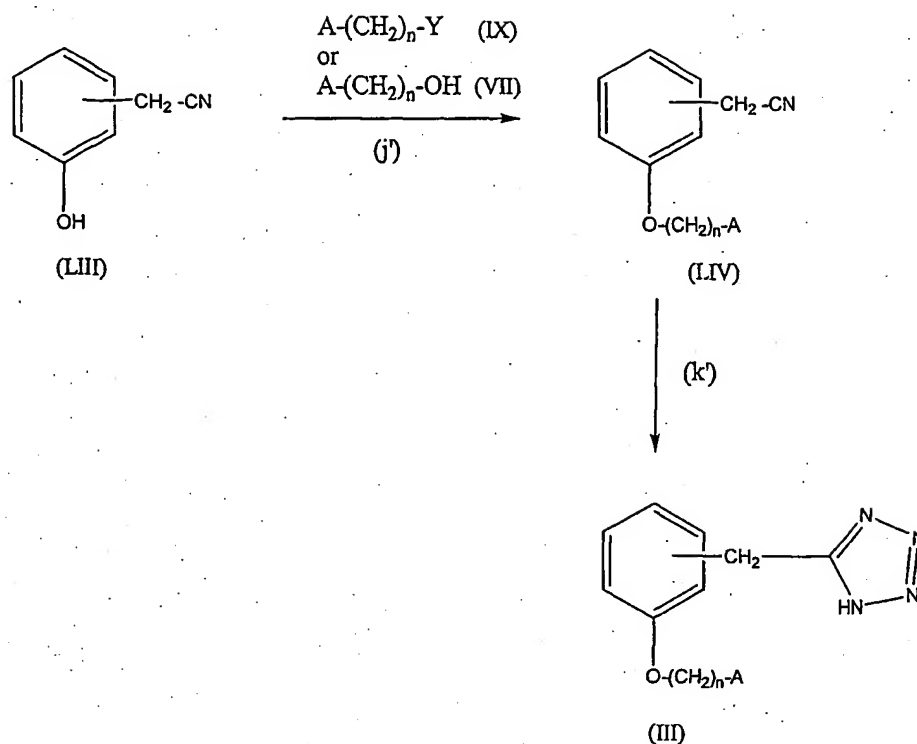


wherein n is 1 or 2 and A is as above, can be prepared from the compound of formula LIII, via reaction scheme in Scheme 18, wherein n, A and Y are as above.

5 In Scheme 18, the compound of formula LIII is converted to the compound of formula LIV in the same manner as described in connection with reaction of step (a) or (b) in Scheme 1.

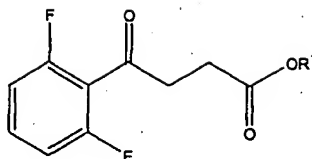
10 The compound of formula LIV is converted to the compound of formula III via reaction of step (k') by heating the compound of formula LIV with sodium azide in the presence of ammonium chloride in dimethylformamide. Any conventional conditions to convert nitrile to terazole can be utilized to carry out this reaction.

Scheme 18



The compound of formula IV

5



wherein  $\text{R}^1$  is as above, can be prepared from 2',6'-difluoroacetophenone  
10 via reaction scheme in Scheme 19.

In Scheme 19,  $\text{R}^6$  is an alkyl group having 1 to 7 carbon atoms.

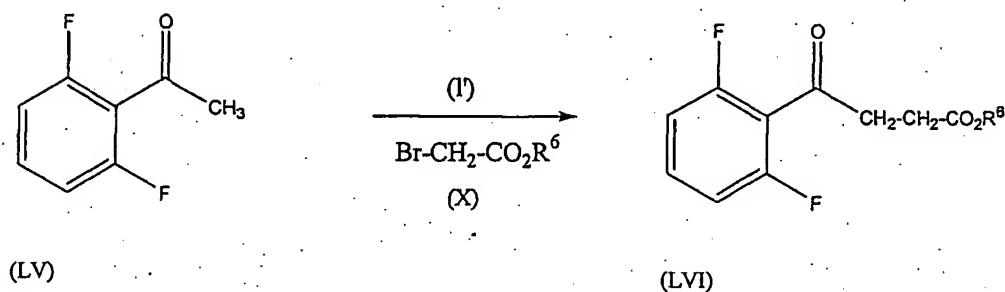
The compound of formula LV is converted to compound of formula LVI via reaction of  
15 step (l') in same manner as described hereinbefore in connection with reaction of step  
(c) in Scheme 1.



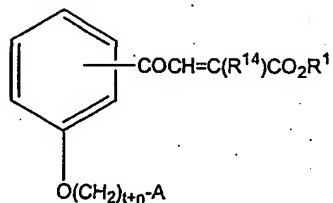
The compound of formula LVI is the compound of formula IV where  $R^1$  is an alkyl group having 1 to 7 carbon atoms. The compound of formula LVI can be converted to the free acid i.e. the compound of formula IV where  $R^1$  is H by ester hydrolysis. Any conventional method of ester hydrolysis will produce the compound of formula IV

5 where  $R^1$  is H.

Scheme 19



The compound of formula V



15 wherein n, A and  $R^1$  are as above,  $R^{14}$  is hydroxy can be prepared from the compound of formula VI, via reaction scheme in Scheme 20.

In Scheme 20, n, A are as above. Y is a leaving group such as halide, mesyloxy or tosyloxy.  $R^7$  is an alkyl group having 1 to 7 carbon atoms and  $R^8$  is an alkyl group having from 1 to 2 carbon atoms.

The compound of formula VI is converted to compound of formula VIII in same manner as described hereinbefore in connection with the reaction of step (a) or (b) of Scheme 1.

The compound of formula VIII is reacted with compound of formula LVII via reaction of step (m') in the presence of freshly prepared sodium alkoxide at room temperature to produce compound of formula LVIII. Any conventional conditions for this alkylation reaction can be utilized to carry out the reaction.

5

The compound of formula LVIII is the compound of formula V where  $R^1$  is an alkyl group having 1 to 2 carbon atoms. The compound of formula LVIII can be converted to the free acid i.e. the compound of formula V where  $R^1$  is H by ester hydrolysis via reaction of step (n'). Any conventional method of ester hydrolysis will produce the

10

compound of formula V where  $R^1$  is H.

The compound of formula LVIII can be converted to compound of formula LIX where  $R^7$  is an alkyl group having 1 to 7 carbon atoms by esterification of carboxylic acid with compound of formula XXX using N,N-dicyclohexylcarbodiimide as dehydrating

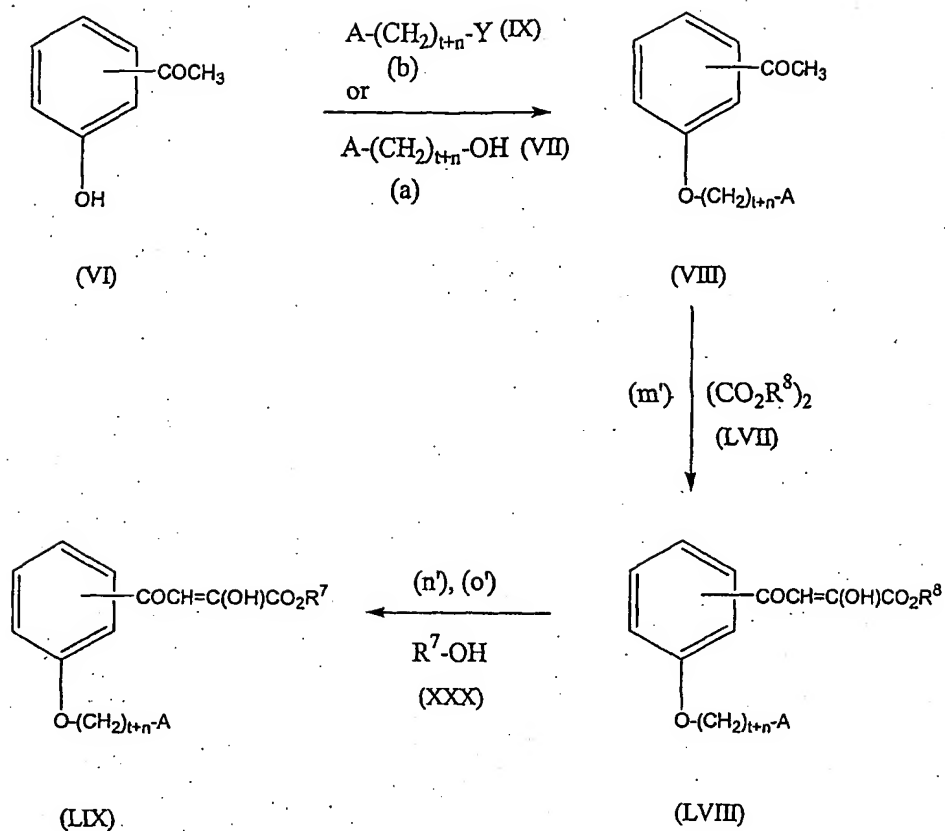
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condensing agent. Any conditions conventional for this reaction can be utilized to carry out the reaction of step (o').

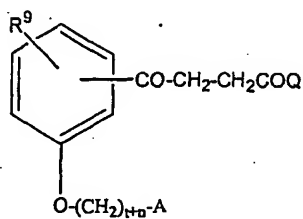
The compound of formula LIX is the compound of formula V where  $R^1$  is an alkyl group having 1 to 7 carbon atoms.

20

Scheme 20

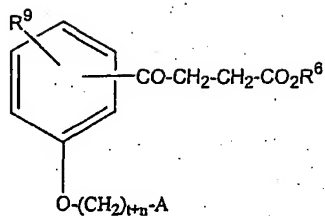


- 5 The compound of formula I' where X is  $-\text{CH}_2\text{CH}_2-$ ,  $\text{R}^9$  is hydrogen, halo, or alkoxy having 1 to 3 carbon atoms, q and m are 0, t is 0 or 1, and n is 1 or 2, i. e. compounds of formula:



XCI

wherein Q is  $\text{NR}^{10}\text{R}^{11}$  where  $\text{R}^{10}$  is hydrogen and  $\text{R}^{11}$  is hydroxyl group. t, n, A, and  $\text{R}^9$  are as described above, can be prepared from the compound of the formula



XI

via the reaction scheme of Scheme 21.

5

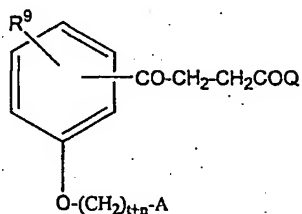
In the reaction scheme 21, A, t, R<sup>9</sup>, R<sup>6</sup> and n are as above.

The compound of formula XI is prepared in the same manner as described in the reaction scheme of Scheme 1.

The compound of formula XI can be converted to the compound of formula XCII via reaction step (s'') by treating the compound of formula XI with hydroxylamine hydrochloride in an organic solvent, for example ethanol, tetrahydrofuran or the like. The reaction is carried out using organic base for example, potassium hydroxide or the like. Any conditions conventional for the synthesis of hydroxamic acids can be utilized to carry out this reaction.

15

The compound of formula I' where X is -CH<sub>2</sub>-CH<sub>2</sub>-, q and m are 0, t is 0 or 1, and n is 1 or 2, R<sup>9</sup> is hydrogen, halo, or alkoxy having 1 to 3 carbon atoms, i. e. compounds of formula:



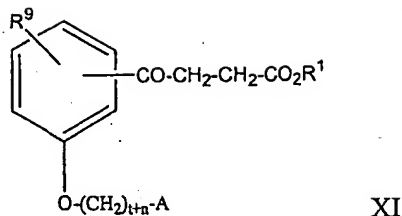
XCIII

20

wherein t, n, A, and R<sup>9</sup> are described as above. Q is NR<sup>10</sup>R<sup>11</sup> where R<sup>10</sup> and R<sup>11</sup> are hydrogen.

can be prepared from the compound of the formula

25



via the reaction scheme in Scheme 21.

5

In the reaction scheme of Scheme 21, A, t, R<sup>9</sup> and n are as above. R<sup>1</sup> is H, R<sup>6</sup> is an alkyl having 1 to 7 carbon atoms.

The compound of formula XI is prepared in the same manner as described in the reaction scheme of Scheme 1. The compound of formula XI is the compound of formula I' where R<sup>1</sup> is an alkyl group containing from 1 to 7 carbon atoms. The compound of formula XI can be converted to the free acid i.e. the compound of formula I' where R<sup>1</sup> is H by ester hydrolysis.

10

The compound of formula XI can be converted to compound of formula XCIII via reaction step (t'') by first activating by for example, benzotriazole-1-yloxytrispyrrolidinophosphonium hexafluorophosphate, or the like in an organic solvent, for example, methylene chloride, N, N-dimethylformamide or the like followed by addition of aqueous ammonium hydroxide or ammonia. The reaction is carried out using organic base for example, triethylamine, diisopropylethylamine or the like.

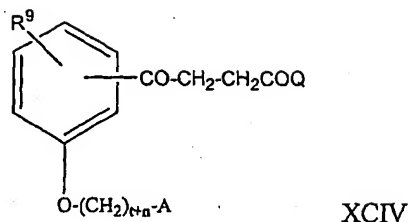
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Any conditions conventional to synthesize amide can be utilized to carry out the reaction of step (t'').

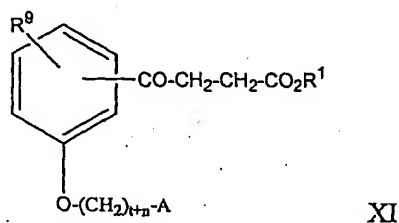
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The compound of formula I' where X is -CH<sub>2</sub>-CH<sub>2</sub>-, q and m are 0, t is 0 or 1, and n is 1 or 2, R<sup>9</sup> is hydrogen, halo, or alkoxy having 1 to 3 carbon atoms, i. e. compounds of formula:

25



wherein t, n, A, and R<sup>9</sup> are described as above. Q is NR<sup>10</sup>R<sup>11</sup> where R<sup>10</sup> and R<sup>11</sup>  
 5 are independently hydrogen or alkyl having 1 to 3 carbon atoms.  
 can be prepared from the compound of the formula



10

via the reaction scheme in Scheme 21.

In the reaction scheme of Scheme 21, A, t, R<sup>9</sup> and n are as above. R<sup>1</sup> is H and R<sup>6</sup> is an  
 15 alkyl having 1 to 7 carbon atoms.

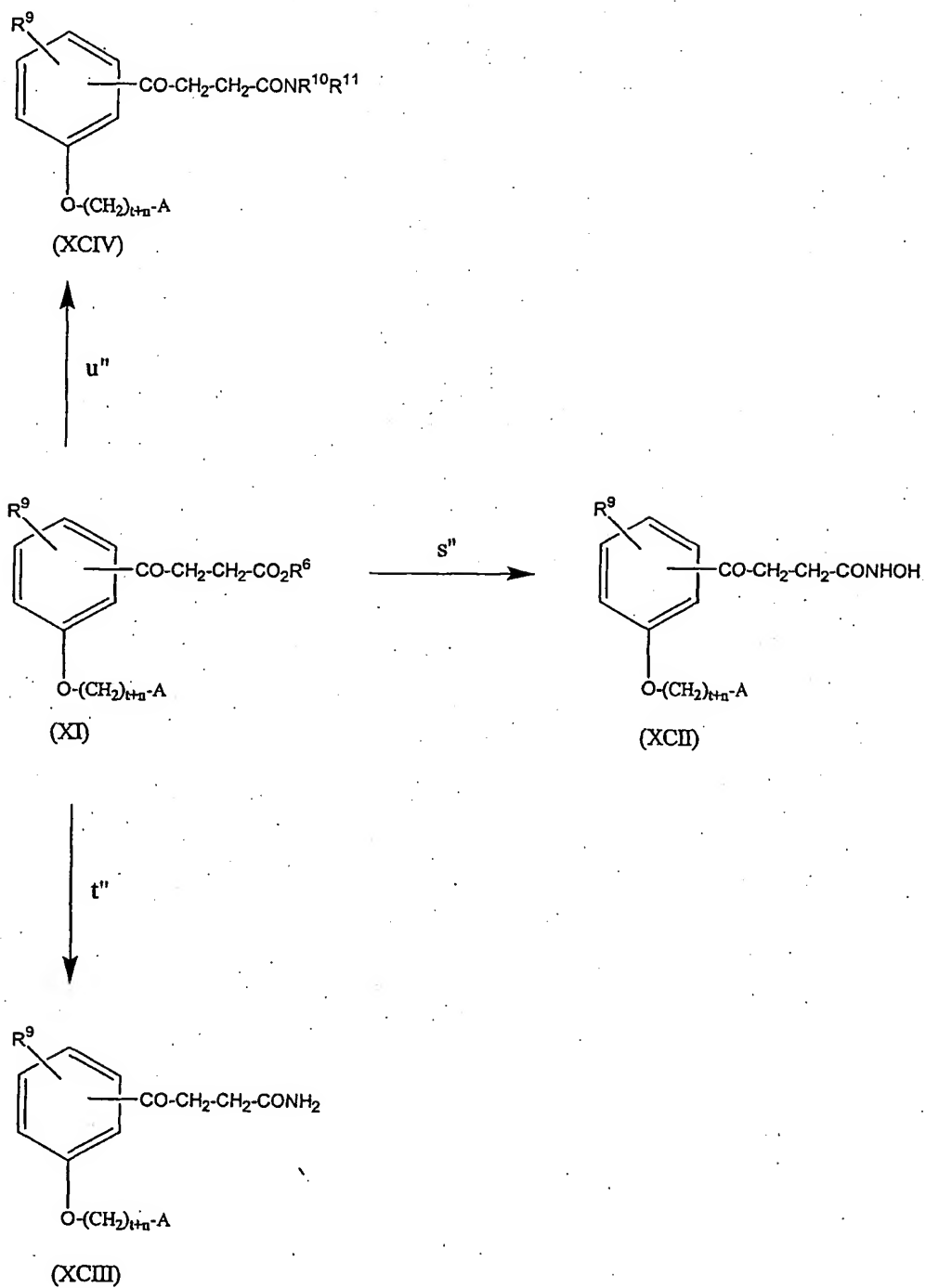
The compound of formula XI is prepared in the same manner as described in the  
 reaction scheme of Scheme 1. The compound of formula XI is the compound of  
 formula I' where R<sup>1</sup> is an alkyl group containing from 1 to 7 carbon atoms. The  
 20 compound of formula XI can be converted to the free acid i.e. the compound of formula  
 I' where R<sup>1</sup> is H by ester hydrolysis.

The compound of formula XI can be converted to the compound of formula XCIV  
 either by first reacting with a chlorinating reagent for example, thionyl chloride or the  
 25 like then reacting acid halide with corresponding amine. Any conventional method of  
 condensing amine with an acid halide can be utilized to carry out the reaction of step

(u'') or by condensing corresponding amine with the compound of formula XI using 1,3-Dicyclohexylcarbodiimide as condensing agent.

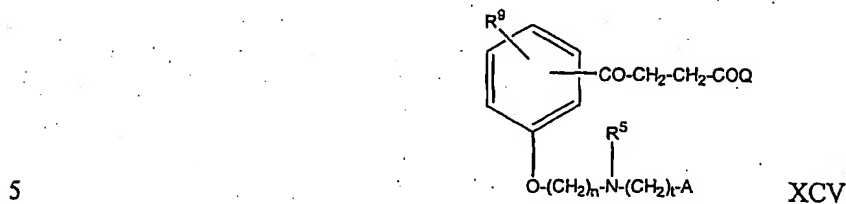
Any conventional method of condensing amine with an acid can be utilized to carry out  
5 the reaction of step (u'').

Scheme 21

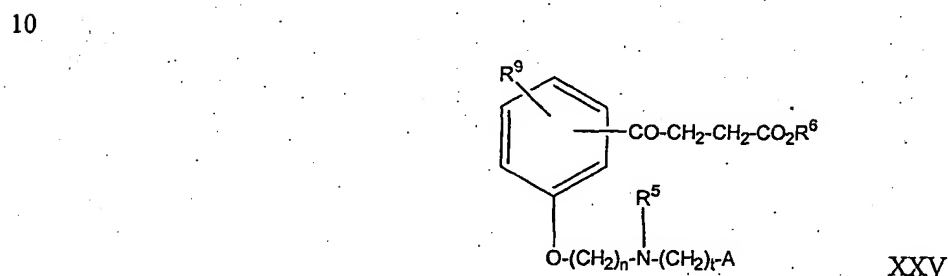




The compound of formula I' where X is  $-\text{CH}_2-\text{CH}_2-$ , q is 1,  $\text{R}^5$  is an alkyl group having 1 to 3 carbon atoms,  $\text{R}^9$  is hydrogen, halo, or alkoxy having 1 to 3 carbon atoms, m is 0, t is 0 or 1, and n is 1 or 2, i. e. compounds of formula:



wherein Q is  $\text{NR}^{10}\text{R}^{11}$  where  $\text{R}^{10}$  is hydrogen and  $\text{R}^{11}$  is hydroxyl group. A, t, n, and  $\text{R}^9$  are as described above, can be prepared from the compound of the formula



via the reaction scheme in Scheme 22.

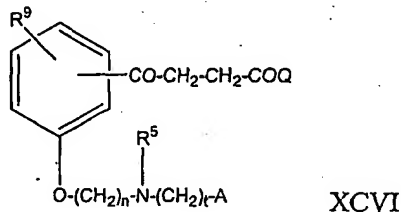
15 In the reaction scheme 22, q, A, t,  $\text{R}^5$ ,  $\text{R}^9$  and n are described as above.  $\text{R}^6$  is an alkyl having 1 to 7 carbon atoms.

The compound of formula XXV is prepared in the same manner as described in the reaction scheme of Scheme 4.

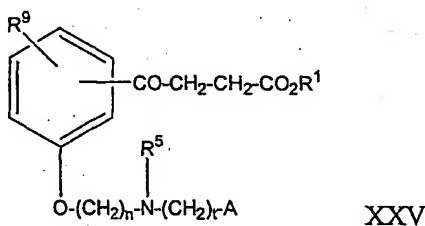
20

The compound of formula XXV can be converted to the compound of formula XCV via reaction step (v'') in the same manner as described in reaction step (s'') of Scheme 21.

The compound of formula I' where X is  $-\text{CH}_2-\text{CH}_2-$ , q is 1,  $\text{R}^5$  is an alkyl group having 1 to 3 carbon atoms,  $\text{R}^9$  is hydrogen, halo, or alkoxy having 1 to 3 carbon atoms, m is 0, t is 0 or 1, and n is 1 or 2,  $\text{R}^1$  is H, i. e. compounds of formula:



wherein q, t, n, A,  $\text{R}^5$  and  $\text{R}^9$  are described as above. Q is  $\text{NR}^{10}\text{R}^{11}$  where  $\text{R}^{10}$  and  $\text{R}^{11}$  are hydrogen and can be prepared from the compound of the formula



via the reaction scheme in Scheme 22.

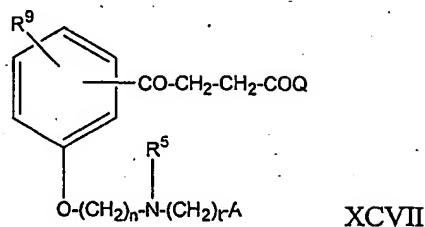
15 In the reaction scheme of Scheme 22, q, A, t,  $\text{R}^5$ ,  $\text{R}^9$  and n are as above.  $\text{R}^1$  is H and  $\text{R}^6$  is an alkyl having 1 to 7 carbon atoms.

The compound of formula XXV is prepared in the same manner as described in the reaction scheme of Scheme 4. The compound of formula XXV is the compound of  
20 formula I' where  $\text{R}^1$  is an alkyl group containing from 1 to 7 carbon atoms. The compound of formula XXV can be converted to the free acid i.e. the compound of formula I' where  $\text{R}^1$  is H by ester hydrolysis.

The compound of formula XXV can be converted to the compound of formula XCVI  
25 via reaction step (w'') in the same manner as described in step (t'') of reaction scheme 21.

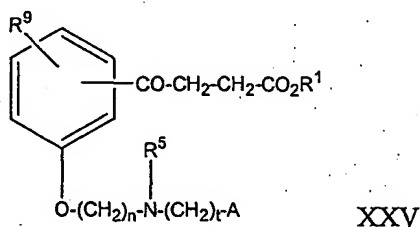
The compound of formula I' where X is  $-\text{CH}_2-\text{CH}_2-$ , q is 1,  $\text{R}^5$  is an alkyl group having 1 to 3 carbon atoms,  $\text{R}^9$  is hydrogen, halo, or alkoxy having 1 to 3 carbon atoms, m is 0, t is 0 or 1, and n is 1 or 2, i. e. compounds of formula:

5



wherein q, t, n, A,  $\text{R}^5$  and  $\text{R}^9$  are as described above, Q is  $\text{NR}^{10}\text{R}^{11}$  where  $\text{R}^{10}$  and  $\text{R}^{11}$  are independently hydrogen or alkyl having 1 to 3 carbon atoms.

10 can be prepared from the compound of the formula



15 via the reaction scheme in Scheme 22.

In the reaction scheme 22, q, A, t,  $\text{R}^5$ ,  $\text{R}^9$  and n are as above.  $\text{R}^6$  is an alkyl having 1 to 7 carbon atoms.  $\text{R}^1$  is H.

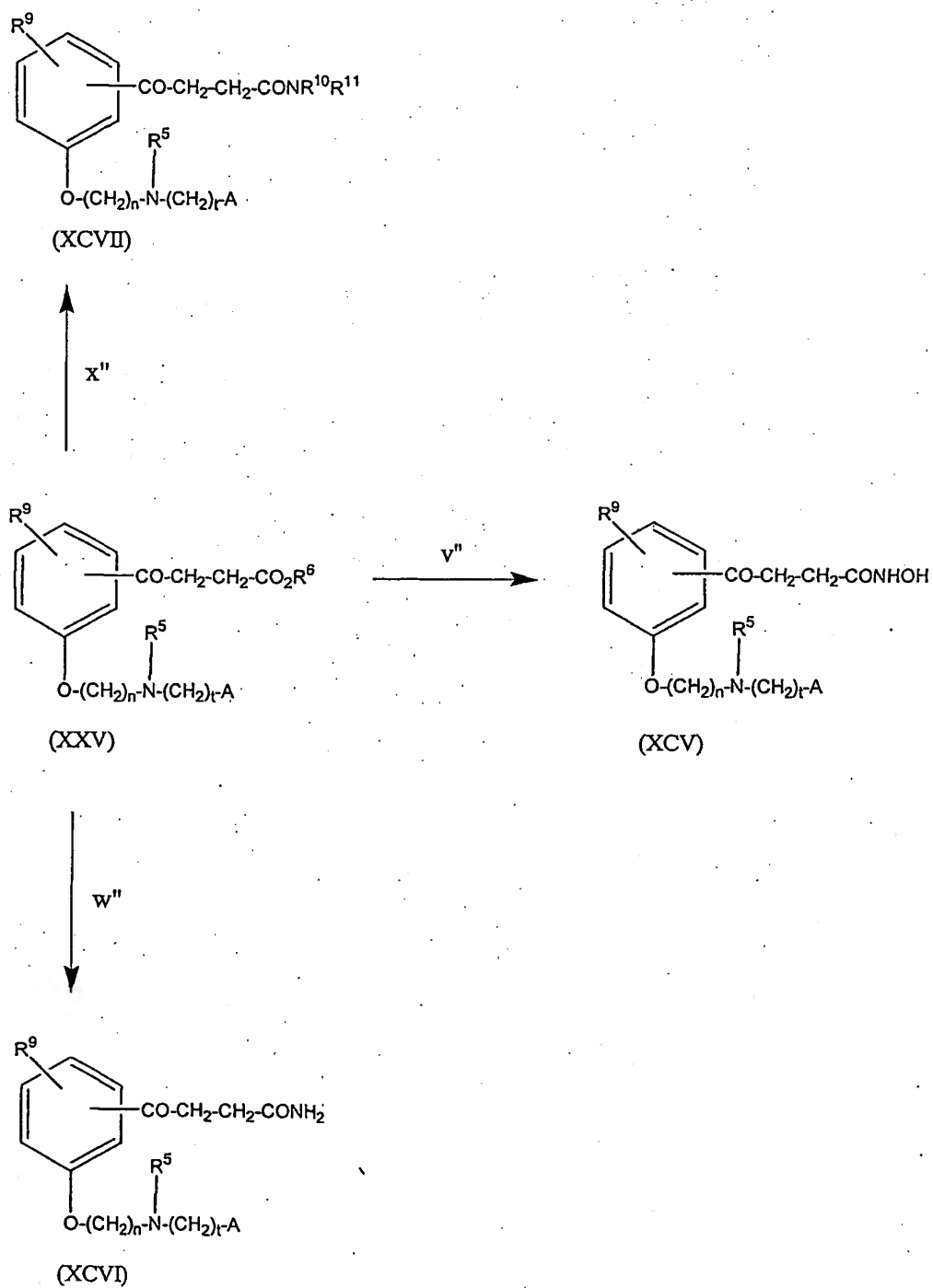
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The compound of formula XXV is prepared in the same manner as described in the reaction scheme of Scheme 4. The compound of formula XXV is the compound of formula I' where  $\text{R}^1$  is an alkyl group containing from 1 to 7 carbon atoms. The compound of formula XXV can be converted to the free acid i.e. the compound of

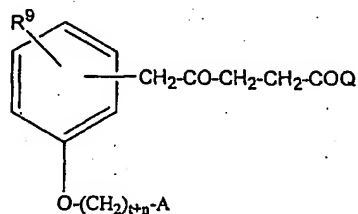
25 formula I' where  $\text{R}^1$  is H by ester hydrolysis.

The compound of formula XXV can be converted to the compound of formula XCVII via reaction step (x'') in the same manner as described in step (u'') of reaction scheme 21.

Scheme 22

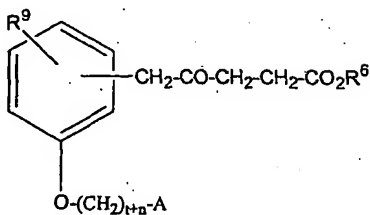


The compound of formula I' where X is  $-\text{CH}_2-\text{CH}_2-$ ,  $\text{R}^9$  is hydrogen, halo, or alkoxy having 1 to 3 carbon atoms, m is 1, q is 0, t is 0 or 1 and n is 1 or 2, i.e. compounds of the formula:



XCVIII

wherein Q is  $\text{NR}^{10}\text{R}^{11}$  where  $\text{R}^{10}$  is hydrogen,  $\text{R}^{11}$  is hydroxyl group. t, n, A, and  $\text{R}^9$  are as described above, can be prepared from the compound of the formula



LXXXV

via the reaction scheme in Scheme 23.

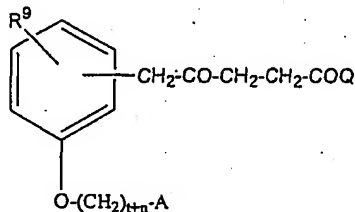
- 15 In the reaction scheme 23, A, t,  $\text{R}^9$  and n are as described above.  $\text{R}^6$  is an alkyl having 1 to 7 carbon atoms.

The compound of formula LXXXV is prepared in the same manner as described in the reaction scheme of Scheme 11.

20

The compound of formula LXXXV can be converted to the compound of formula XCVIII via reaction step (y'') in the same manner as described in reaction step (s'') of Scheme 21.

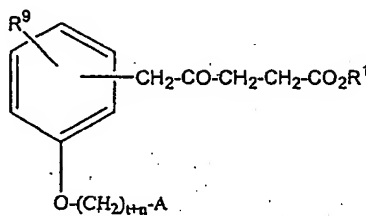
The compound of formula I' where X is  $-\text{CH}_2-\text{CH}_2-$ ,  $\text{R}^9$  is hydrogen, halo, or alkoxy having 1 to 3 carbon atoms, m is 1, q is 0, t is 0 or 1 and n is 1 or 2, i.e. compounds of the formula:



XCIX

wherein t, n, A, and  $\text{R}^9$  are described as above. Q is  $\text{NR}^{10}\text{R}^{11}$  where  $\text{R}^{10}$  and  $\text{R}^{11}$  are hydrogen.

can be prepared from the compound of the formula



LXXXV

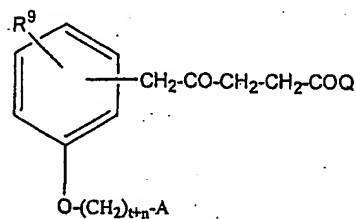
via the reaction scheme in Scheme 23.

In the reaction scheme of Scheme 23, A, t,  $\text{R}^9$ , and n are as above.  $\text{R}^1$  is H.  $\text{R}^6$  is an alkyl having 1 to 7 carbon atoms.

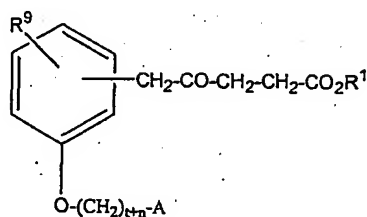
The compound of formula LXXXV is prepared in the same manner as described in the reaction scheme of Scheme 11. The compound of formula LXXXV is the compound of formula I' where  $\text{R}^1$  is an alkyl group containing from 1 to 7 carbon atoms. The compound of formula LXXXV can be converted to the free acid i.e. the compound of formula I' where  $\text{R}^1$  is H by ester hydrolysis.

The compound of formula LXXXV can be converted to the compound of formula XCIX via reaction step (z'') in the same manner as described in reaction step (t'') of reaction scheme 21.

The compound of formula I' where X is  $-\text{CH}_2-\text{CH}_2-$ ,  $\text{R}^9$  is hydrogen, halo, or alkoxy having 1 to 3 carbon atoms, m is 1, q is 0, t is 0 or 1 and n is 1 or 2, i.e. compounds of the formula:



wherein t, n, A, and  $\text{R}^9$  are as described above, Q is  $\text{NR}^{10}\text{R}^{11}$  where  $\text{R}^{10}$  and  $\text{R}^{11}$  are independently hydrogen or alkyl having 1 to 3 carbon atoms. can be prepared from the compound of the formula



via the reaction scheme in Scheme 23.

In the reaction scheme 23, A, t,  $\text{R}^9$  and n are as above.  $\text{R}^1$  is H.  $\text{R}^6$  is an alkyl having 1 to 7 carbon atoms.

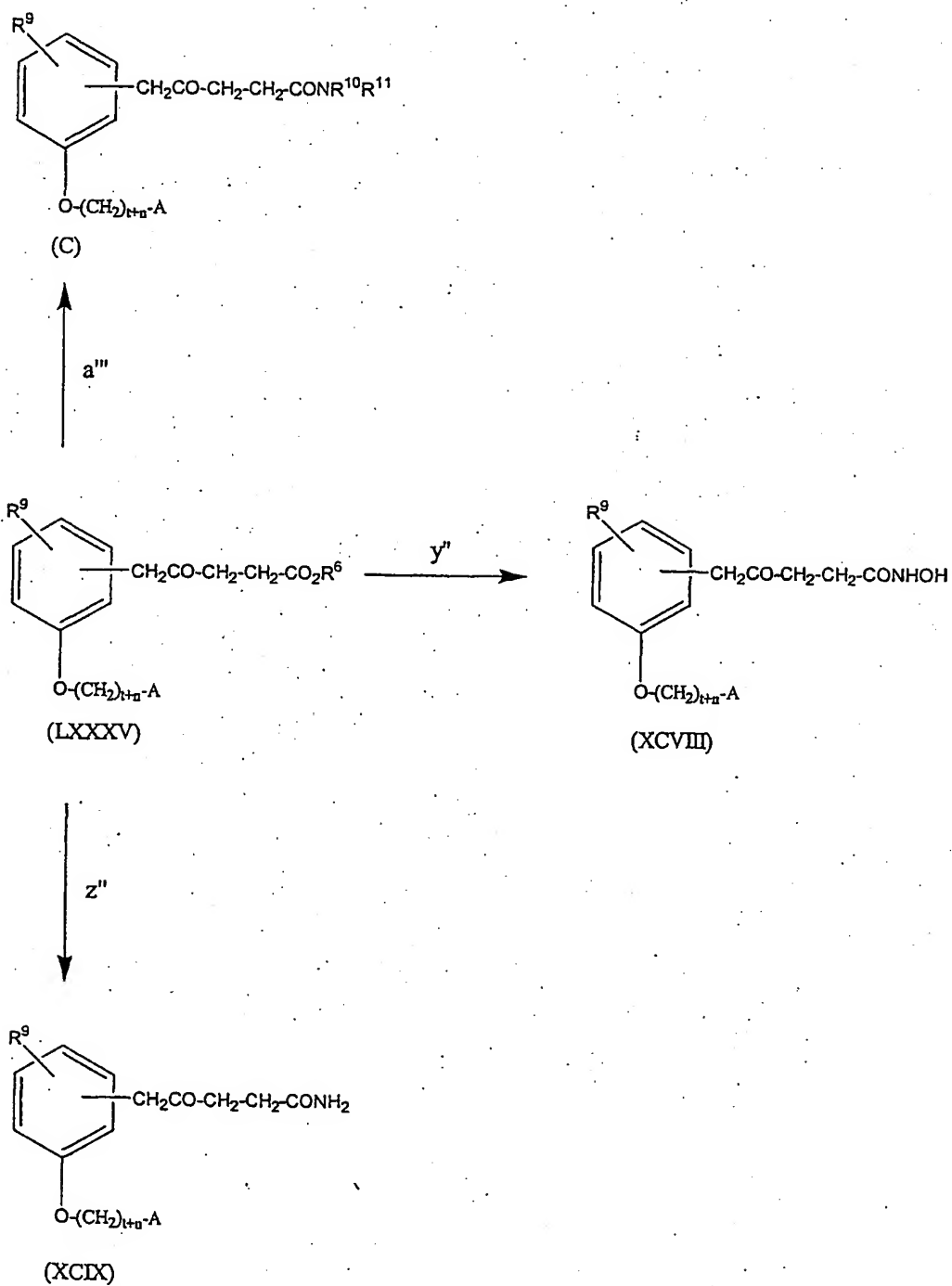
The compound of formula LXXXV is prepared in the same manner as described in the reaction scheme of Scheme 11. The compound of formula LXXXV is the compound of formula I' where  $\text{R}^1$  is an alkyl group containing from 1 to 7 carbon atoms. The

compound of formula LXXXV can be converted to the free acid i.e. the compound of formula I' where  $\text{R}^1$  is H by ester hydrolysis.

The compound of formula LXXXV can be converted to the compound of formula C via reaction step (a''') in the same manner as described in step (u'') of reaction scheme 21.

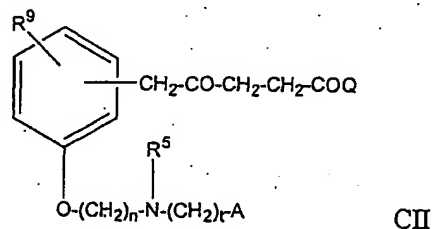


Scheme 23



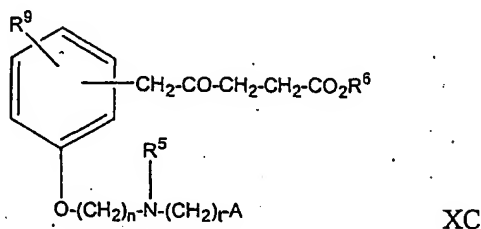
The compound of formula I' where X is  $-\text{CH}_2-\text{CH}_2-$ ,  $\text{R}^9$  is hydrogen, halo, or alkoxy having 1 to 3 carbon atoms, q is 1,  $\text{R}^5$  is an alkyl group having 1 to 3 carbon atoms, m is 1, t is 0 or 1, and n is 1 or 2, i. e. compounds of formula:

5



wherein Q is  $\text{NR}^{10}\text{R}^{11}$  where  $\text{R}^{10}$  is hydrogen and  $\text{R}^{11}$  is hydroxyl group. t, n, A,  $\text{R}^5$  and  $\text{R}^9$  are as described above,

10 can be prepared from the compound of the formula



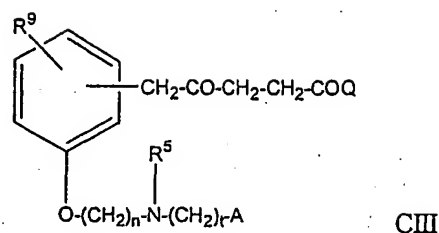
15 via the reaction scheme in Scheme 24.

In the reaction scheme 24, q, A, t, n,  $\text{R}^5$ ,  $\text{R}^9$ , and  $\text{R}^6$  are described as above.

The compound of formula XC is prepared in the same manner as described in the  
20 reaction scheme of Scheme 13.

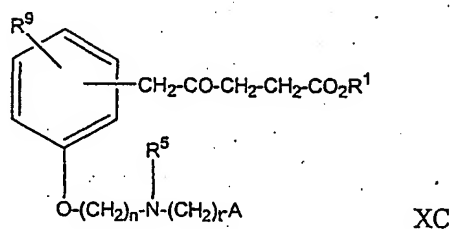
The compound of formula XC can be converted to the compound of formula CII via reaction step (b'') in the same manner as described in reaction step (s'') of Scheme 21.

The compound of formula I' where X is  $-\text{CH}_2-\text{CH}_2-$ ,  $\text{R}^9$  is hydrogen, halo, or alkoxy  
25 having 1 to 3 carbon atoms, q is 1,  $\text{R}^5$  is an alkyl group having 1 to 3 carbon atoms, m is 1, t is 0 or 1, and n is 1 or 2, i. e. compounds of formula:



wherein q, t, n, A, R<sup>5</sup> and R<sup>9</sup> are described as above. Q is NR<sup>10</sup>R<sup>11</sup> where R<sup>10</sup> and R<sup>11</sup> are hydrogen.

can be prepared from the compound of the formula



via the reaction scheme in Scheme 24.

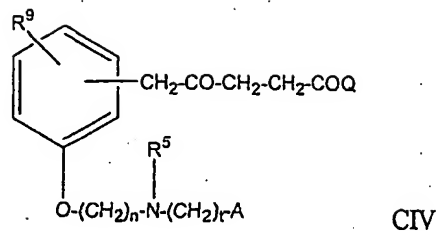
In the reaction scheme of Scheme 24, q, A, t, R<sup>5</sup>, R<sup>9</sup> and n are as above. R<sup>1</sup> is H. R<sup>6</sup> is an alkyl having 1 to 7 carbon atoms.

The compound of formula XC is prepared in the same manner as described in the reaction scheme of Scheme 13. The compound of formula XC is the compound of formula I' where R<sup>1</sup> is an alkyl group containing from 1 to 7 carbon atoms. The compound of formula XC can be converted to the free acid i.e. the compound of formula I' where R<sup>1</sup> is H by ester hydrolysis.

20

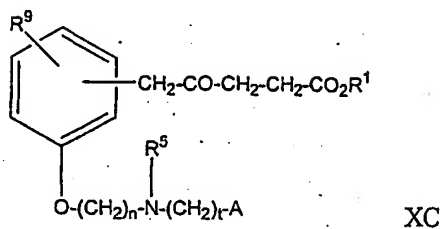
The compound of formula XC can be converted to the compound of formula CIII via reaction step (c'') in the same manner as described in step (t'') of reaction scheme 21.

The compound of formula I' where X is -CH<sub>2</sub>-CH<sub>2</sub>-, R<sup>9</sup> is hydrogen, halo, or alkoxy having 1 to 3 carbon atoms, q is 1, R<sup>5</sup> is an alkyl group having 1 to 3 carbon atoms, m is 1, t is 0 or 1, and n is 1 or 2, i. e. compounds of formula:



wherein q, t, n, A, R<sup>5</sup> and R<sup>9</sup> are as described above, Q is NR<sup>10</sup>R<sup>11</sup> where R<sup>10</sup> and R<sup>11</sup> are independently hydrogen or alkyl having 1 to 3 carbon atoms.

5 can be prepared from the compound of the formula



10 via the reaction scheme in Scheme 24.

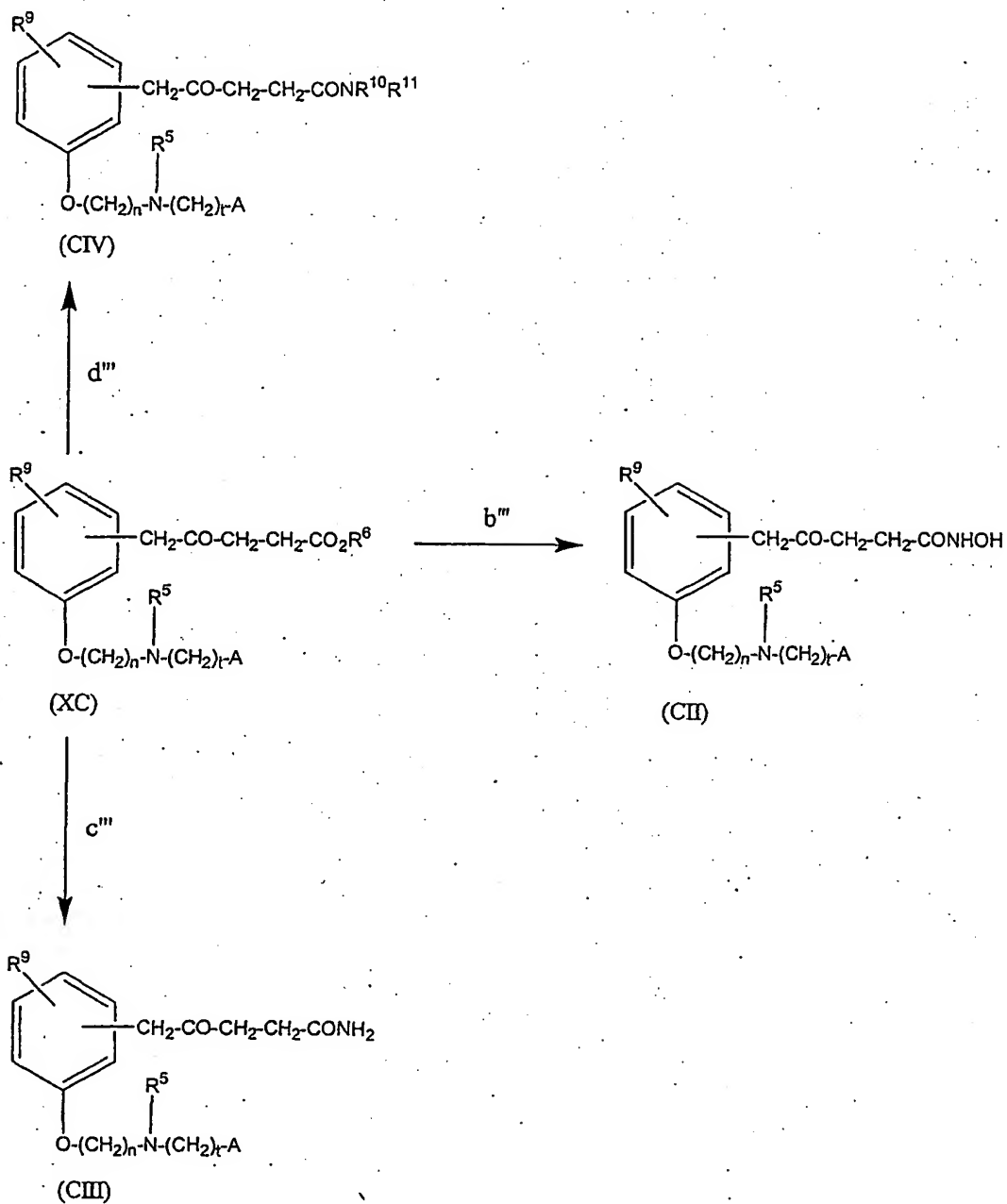
In the reaction scheme 24, q, A, t, R<sup>5</sup>, R<sup>9</sup> and n are as above. R<sup>1</sup> is H. R<sup>6</sup> is an alkyl having 1 to 7 carbon atoms.

15 The compound of formula XC is prepared in the same manner as described in the reaction scheme of Scheme 13. The compound of formula XC is the compound of formula I' where R<sup>1</sup> is an alkyl group containing from 1 to 7 carbon atoms. The compound of formula XC can be converted to the free acid i.e. the compound of formula I' where R<sup>1</sup> is H by ester hydrolysis.

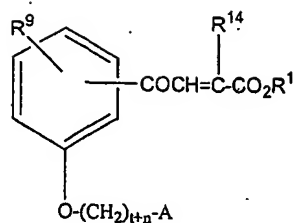
20

The compound of formula XC can be converted to the compound of formula CIV via reaction step (d''') in the same manner as described in step (u'') of reaction scheme 21.

Scheme 24



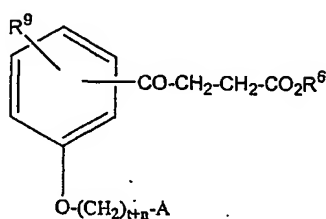
The compound of formula V' where n is 1 or 2, t is 0,  $R^1$ ,  $R^9$  and  $R^{14}$  are H, i. e. compounds of formula:



CVI

wherein  $t$ ,  $n$ ,  $A$ ,  $R^9$ ,  $R^{14}$  and  $R^1$  are as described above,  
can be prepared from the compound of the formula

5



XI

10 via the reaction scheme in Scheme 25.

In the reaction scheme of Scheme 25,  $A$ ,  $t$ , and  $n$  are as above.  $R^6$  is an alkyl group containing from 1 to 7 carbon atoms.

15 The compound of formula XI is prepared in the same manner as described in the reaction scheme of Scheme 1.

The compound of formula XI can be converted to compound of formula CV via reaction step (e'''), by treating the compound of formula XI with bromine or the like in an organic solvent, for example ether, carbon tetrachloride with the preferred organic solvent being ether.

As the reaction temperature, ice cooling to room temperature can be used with the preferred being ice cooling.

25

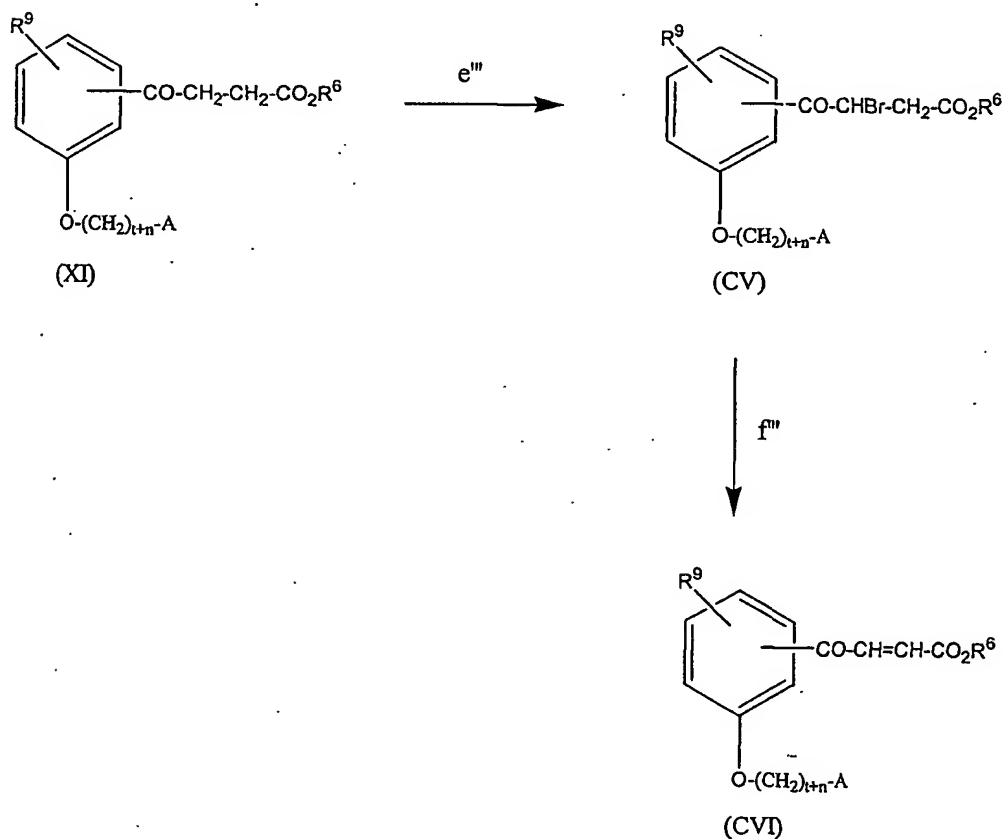
The compound of formula CV can be converted to the compound of formula CVI via reaction step (f'''), by dehydrobromination. The reaction is carried out using conventional base preferred base being triethylamine or the like in an organic solvent for example carbon tetrachloride or the like. Any of the conditions conventional in

5 dehydrobromination can be utilized to carry out the reaction of step (f''').

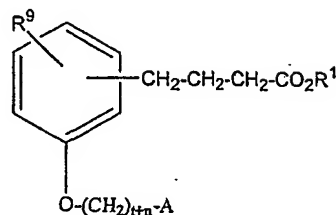
The compound of formula CVI is the compound of formula V' where R<sup>1</sup> is an alkyl group containing from 1 to 7 carbon atoms. The compound of formula CVI can be converted to the free acid i.e. the compound of formula V' where R<sup>1</sup> is H by ester

10 hydrolysis. Any conventional method of ester hydrolysis will produce the compound of formula V' where R<sup>1</sup> is H.

Scheme 25



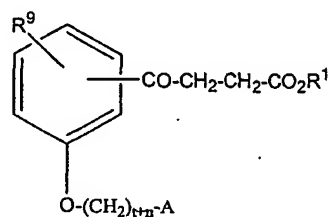
The compound of formula CXVI where X is  $-\text{CH}_2-\text{CH}_2-$ , t is 0 or 1, and n is 1 or 2,  $\text{R}^1$  and  $\text{R}^9$  are H, i. e. compounds of formula:



5

CVII

wherein t, n, A, and  $\text{R}^9$  are as described above,  $\text{R}^1$  is H.  
can be prepared from the compound of the formula



10

XI

via the reaction scheme in Scheme 26.

15

In the reaction scheme of 26, A, t, n and  $\text{R}^9$  are as above.  $\text{R}^1$  is H.  $\text{R}^6$  is an alkyl group having 1 to 7 carbon atoms.

20

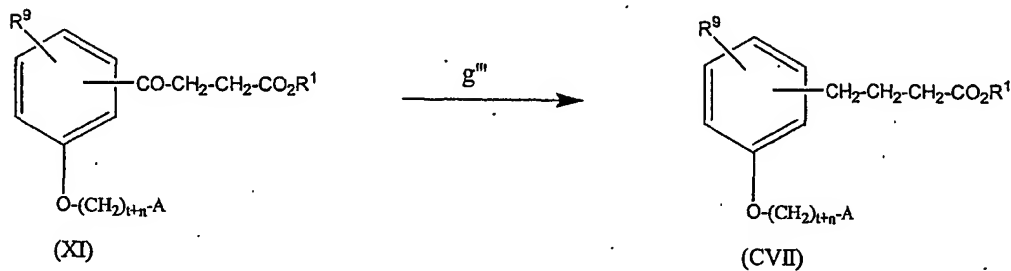
The compound of formula XI is prepared in the same manner as described in the reaction scheme of Scheme 1. The compound of formula XI is the compound of formula I' where  $\text{R}^1$  is an alkyl group containing from 1 to 7 carbon atoms. The compound of formula XI can be converted to the free acid i.e. the compound of formula I' where  $\text{R}^1$  is H by ester hydrolysis. Any conventional method of ester hydrolysis will produce the compound of formula I' where  $\text{R}^1$  is H.

25

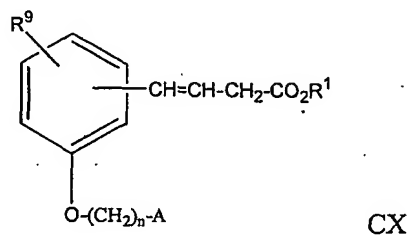


- The compound of formula XI is converted to compound of formula CVII via reaction step (g''') via Wolff-Kishner reduction by treating the compound of formula XI with hydrazine hydrate and potassium hydroxide in an organic solvent for example, ethylene glycol or the like. Any of the conditions conventional in Wolff-Kishner reductions can be utilized to carry out the reaction of step (g''').

Scheme 26

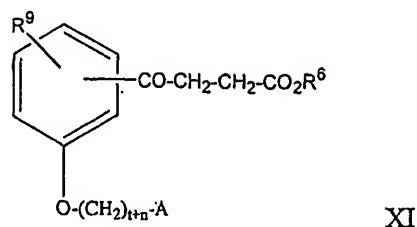


- 10 The compound of formula CXI where n is 1 or 2, R<sup>9</sup> is H and R<sup>1</sup> is hydrogen or alkyl having 1 to 3 carbon atoms, i.e. compounds of formula:



15

wherein n, A, R<sup>9</sup> and R<sup>1</sup> are as described above,  
can be prepared from the compound of the formula



via the reaction scheme in Scheme 27.

5

In the reaction scheme of Scheme 27,  $R^9$  is a hydrogen atom,  $t$  is 0,  $R^6$  is an alkyl having 1 to 7 carbon atoms,  $A$  and  $n$  are as described above.

10 The compound of formula XI is prepared in the same manner as described in the reaction scheme of Scheme 1.

15 The compound of formula XI can be converted to the compound of formula CVIII via reaction step (h'') by selectively reducing ketone group to an alcohol. This reaction is carried out utilizing conventional reducing agents for example, sodium borohydride in ethanol, Bis-3-methyl-2-butyl-borane in tetrahydrofuran or the like. Any of the conditions conventional in such selective reduction reactions can be utilized to carry out the reaction of step (h'').

20 The compound of formula CVIII can be converted to compound of formula CIX via reaction step (i'') by bromination of compound of formula CVIII with brominating reagents for example, phosphorous tribromide in tetrahydrofuran or dioxane, hydrogen bromide in acetic acid or dioxane, carbon tetrabromide and bis-(1,2-diphenylphosphino)ethane or the like. Any of the conditions conventional in such bromination reactions can be utilized to carry out the reaction of step (i'').

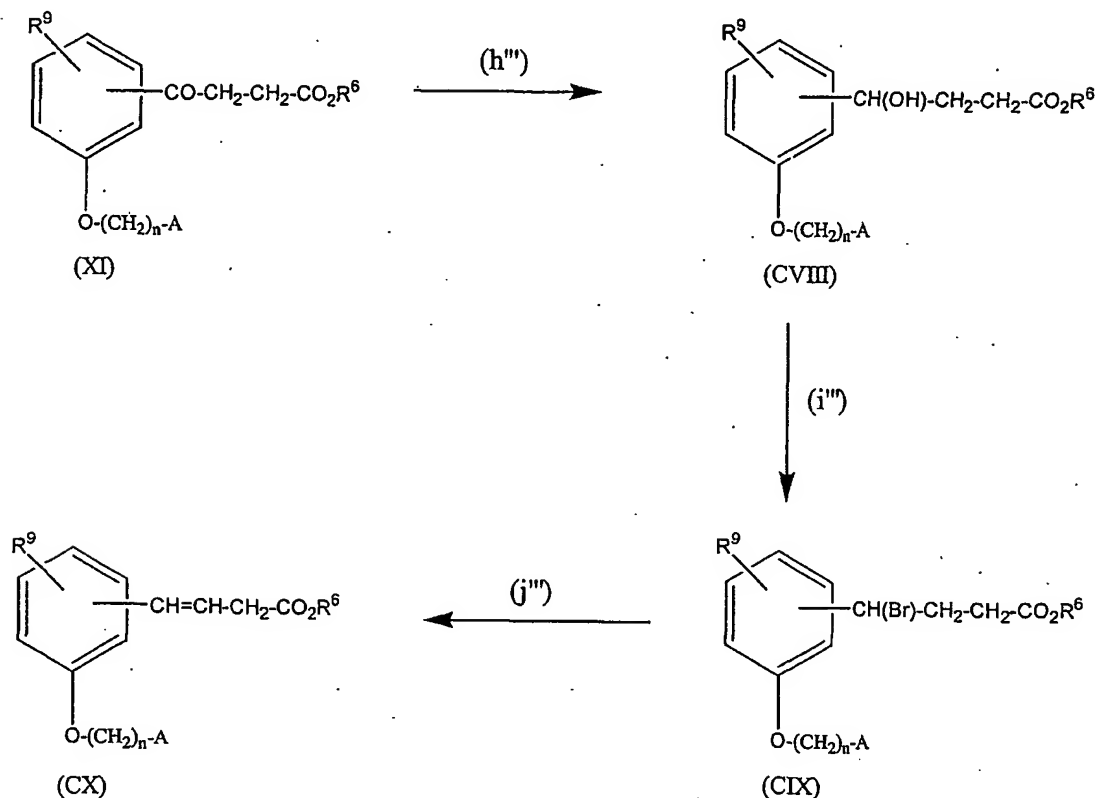
25

The compound of formula CIX can be converted to the compound of formula CX via reaction step (j''), by dehydrobromination. The reaction is carried out using conventional base preferred base being triethylamine or the like in an organic solvent for example carbon tetrachloride or the like. Any of the conditions conventional in  
30 such dehydrobromination reactions can be utilized to carry out the reaction of step (j'').

The compound of formula CX is the compound of formula XCI where  $R^1$  is an alkyl group containing from 1 to 3 carbon atoms. The compound of formula CX can be converted to the free acid i.e. the compound of formula XCI where  $R^1$  is H by ester hydrolysis. Any conventional method of ester hydrolysis will produce the compound of

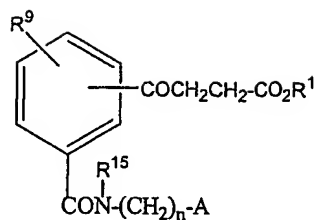
5 formula XCI where  $R^1$  is H.

Scheme 27



The compound of formula CXVII where X is  $-CH_2-CH_2-$ , and n is 0 or 2,  $R^{15}$  is a

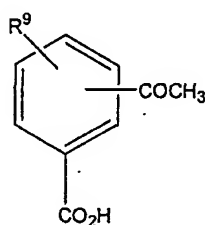
10 hydrogen or lower alkyl group having 1 to 3 carbon atoms,  $R^9$  is hydroxy, hydrogen, alkoxy group having 1 to 3 carbon atoms, halogen atom,  $R^1$  is hydrogen or alkyl having 1 to 3 carbon atoms, i. e. compounds of formula:



CXIV

wherein  $n$ ,  $A$ ,  $R^9$  and  $R^{15}$  are as described above,  
can be prepared by reacting the compound of the formula

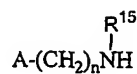
5



CXI

with compound of formula

10



CXII

via the reaction scheme in Scheme 28.

- 15 In the reaction scheme of Scheme 28,  $A$ ,  $n$ ,  $R^9$ ,  $R^{15}$  are described as above,  $R^6$  is an alkyl having 1 to 3 carbon atoms.

The compound of formula CXI can be converted to compound of formula CXIII via reaction step (k'') by treating compound of formula CXI with condensing agent, for example diethyl cyanophosphate, 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide or

- 20 the like in an organic solvent, for example, methylene chloride,  $N,N$ -dimethylformamide followed by addition of compound of formula CXII.

The reaction temperature can be from  $0^\circ\text{C}$  to room temperature.

The compound of formula CXIII can be converted to the compound of formula CXIV via reaction of step (l''') by alkylating the compound of formula CXIII with the compound of formula X. This reaction is carried out in the same manner as described in the reaction step (c) of reaction scheme 1.

5

The compound of formula CXIV is the compound of formula CXVII where  $R^9$  is an alkoxy group having 1 to 3 carbon atoms, halogen atom. The  $R^9$  can be converted to hydroxy via demethylation by using for example, boron tribromide in methylene chloride or the like. Any of the conditions conventional in such demethylation reactions

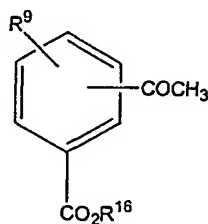
10

The compound of formula CXIV is the compound of formula CXVII where  $R^1$  is an alkyl group having 1 to 3 carbon atoms. The compound of formula CXIV can be converted to the free acid i.e. the compound of formula CXVII where  $R^1$  is H by ester

15

hydrolysis. Any conventional method of ester hydrolysis will produce the compound of formula CXVII where  $R^1$  is H.

20



wherein  $R^{16}$  is a lower alkyl group having 1 to 3 carbon atoms.  $R^9$  is a hydroxyl group.

25

The reaction between compound of formula CI and alkyl halide can be carried like in an organic solvent, for example N, N-dimethylformamide or the like, using base, for example potassium carbonate, cesium carbonate or the like. Any of the conditions conventional in such alkylation reactions can be utilized to carry out this reaction. Ester

hydrolysis can be conducted under acidic conditions for example, hydrochloric acid or hydrochloric acid mixed with organic solvent for example, ethanol or using acetic acid or the like. The reaction can be carried out at room temperature to solvent refluxing temperature. Any conventional conditions for acidic ester hydrolysis can be utilized to carry out this reaction. Further, if needed, ester hydrolysis can be carried out using basic conditions, for example, in an aqueous solution of sodium hydroxide or a mixed solution of sodium hydroxide in an organic solvent for example, ethanol or the like. Any conditions conventional for basic hydrolysis can be utilized to carry out this reaction

10

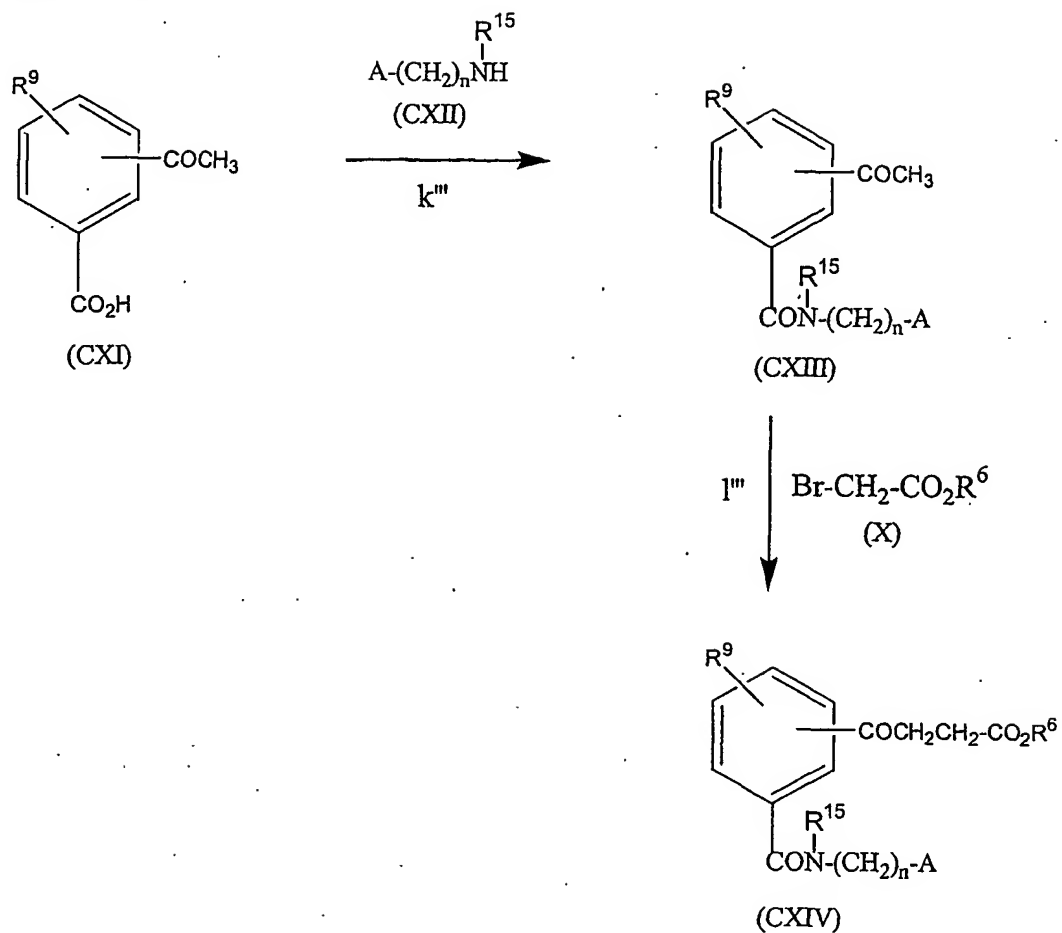
Compounds of general formula CXII can be prepared by reacting compound of formula VII with chlorinating agent for example, trimethylsilyl chloride, thionyl chloride or the like in an organic solvent for example, dimethyl sulfoxide, N, N-dimethylformamide or the like. The reaction temperature can be room temperature to organic refluxing temperature. Any conditions conventional for chlorination reactions can be utilized to carry out the reaction.

15

The chloromethyl intermediate was converted to compound of formula CXII via Gabriel synthesis by treating chloromethyl intermediate with potassium phthalimide in an organic solvent for example, N, N-dimethylformamide, dioxane or the like. The phthalimide is then reacted with hydrazine by an exchange reaction in an organic solvent for example, ethanol, dioxane or the like to produce the compound of formula CXII. Any of the conditions conventionally used in the Gabriel synthesis can be utilized to carry out the reaction.

25

Scheme 28



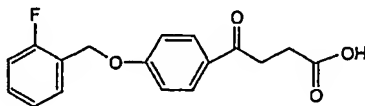
The invention will be better understood by reference to the following examples which illustrate but do not limit the invention described herein.

5

#### CHEMICAL SYNTHESIS EXAMPLES

EXAMPLE 1: Synthesis of 4-(4-(2-Fluorobenzoyloxy)phenyl)-4-oxobutyrac acid

10



Step A: Preparation of 4-(2-Fluorobenzoyloxy)acetophenone:

A solution of 4-Hydroxyacetophenone (2.80 g, 20.6 mmol) in dry DMF (15 ml) was added at room temperature to a suspension of NaH (60% in oil, .794 g) in dry DMF (20 ml). When evolution of hydrogen ceased, 2-Fluorobenzyl bromide (3 g, 15.8 mmol) was added drop wise. The reaction mixture was stirred at room temperature for 6 hours, quenched with sat aq.  $\text{NH}_4\text{Cl}$  and concentrated in vacuo. The crude residue was taken in EtOAc and washed with water and brine. The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated. The residue was purified by flash chromatography on silica gel column (hex: ethyl acetate, 2:1) to provide the title compound as an off white solid.

$^1\text{H}$  NMR (270 MHz,  $\text{CDCl}_3$ ): 2.5 (s, 3H); 5.2 (s, 2H); 6.9-7.1 (m, 4H); 7.2-7.3 (m, 1H); 7.4 (t, 1H); 7.9 (d, 2H).

Step B: Preparation of tert-Butyl 4-(4-(2-fluorobenzoyloxy)phenyl)-4-oxobutyrate:

To a stirred solution of 4-(2-fluorobenzoyloxy)acetophenone (Step A, 1.5 g, 6.1 mmol) in dry THF (20 ml) and DMPU (5 ml) was added a solution of lithium bis(trimethylsilyl)amide (1.0M, 7 ml) at  $-60^\circ\text{C}$  under argon. After 10 minutes of stirring at  $-60^\circ\text{C}$ , tert-Butyl bromoacetate (4.75 g, 24.4 mmol) was added rapidly. The reaction mixture was stirred for an additional 10 minutes and then warmed to room temperature for 4 hours. The crude mixture was taken in EtOAc and washed with water and brine. The aqueous layer was extracted one more time with EtOAc. The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ , filtered, concentrated and purified by flash chromatography on a silica gel column (hex: ethyl acetate, 2:1) to provide the title compound.

$^1\text{H}$  NMR (270 MHz,  $\text{CDCl}_3$ ): 1.4 (s, 9H); 2.7 (t, 2H); 3.2 (t, 2H); 5.1 (s, 2H); 6.9-7.1 (m, 4H); 7.2-7.3 (m, 1H); 7.4 (t, 1H); 7.9 (d, 2H).

Step C: Preparation of 4-(4-(2-Fluorobenzoyloxy)phenyl)-4-oxobutyric acid:

A solution of tert-Butyl 4-(4-(2-fluorobenzoyloxy)phenyl)-4-oxobutyrate (Step B, 1.27 g, 4.2 mmol) in dichloromethane (25 ml) was treated with trifluoroacetic acid (5 ml). The reaction mixture was stirred at ambient temperature for 3 hours and concentrated in

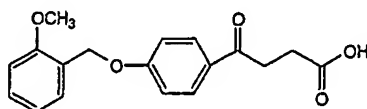


vacuo. The purification was done by flash chromatography on silica gel column (chloroform: methanol, 95:5 spiked with acetic acid) to afford the title compound as a white powder.

- 5  $^1\text{H}$  NMR (270 MHz,  $\text{CDCl}_3:\text{CD}_3\text{OD}$ ): 2.6 (t, 2H); 3.2 (t, 2H); 5.1 (s, 2H); 6.9-7.1 (m, 4H); 7.2-7.3 (m, 1H); 7.4 (t, 2H); 7.9 (d, 2H).

EXAMPLE 2: Synthesis of 4-(4-(2-Methoxybenzyloxy)phenyl)-4-oxobutyrac acid

10



Step A: Preparation of 4-(2-Methoxybenzyloxy)acetophenone:

- 15 A solution of 2-Methoxybenzyl alcohol (2.99 g, 21.7 mmol) in dry THF (5 ml) and dry DMF (5 ml) was added to a stirred solution of 4-Hydroxyacetophenone (3.25 g, 23.8 mmol), triphenylphosphine (7.36 g, 28.0 mmol), and diethyl azodicarboxylate (4.51 g, 25.9 mmol) in dry THF (20 ml) at 5-10°C. The reaction mixture was stirred at 0°C for 2 hours, warmed to room temperature and concentrated in vacuo. The residue was
- 20 taken in EtOAc and washed twice with saturated  $\text{NaHCO}_3$ . The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered, concentrated and purified by flash chromatography on a silica gel column (chloroform: methanol, 99:1) to provide the title compound as a white solid.
- 25  $^1\text{H}$  NMR (270 MHz,  $\text{CDCl}_3$ ): 2.5 (s, 3H); 3.9 (s, 3H); 5.2 (s, 2H); 6.9-7.1 (m, 4H); 7.3 (m, 1H); 7.4 (d, 1H); 7.9 (d, 2H).

Step B: Preparation of Ethyl 4-(4-(2-methoxybenzyloxy)phenyl)-4-oxobutyrac:

- 30 To a stirred solution of 4-(2-Methoxybenzyloxy)acetophenone (Step A, 1.22 g, 4.7 mmol) in dry THF (20 ml) and DMPU (5 ml) was added a solution of lithium bis(trimethylsilyl)amide (1.0M, 5 ml) under argon at -60°C. After 10 minutes of

stirring at  $-60^{\circ}\text{C}$ , ethyl bromoacetate (2.59 g, 15.6 mmol) was added rapidly. The reaction mixture was stirred for an additional 10 minutes and then warmed to room temperature for 2 hours. The crude mixture was taken in EtOAc and washed with water. The aqueous layer was extracted one more time with EtOAc and combined  
5 organic layers were dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated. The purification was done by flash chromatography on silica gel column (hex: ethyl acetate, 4:1) to provide the title compound as a white solid.

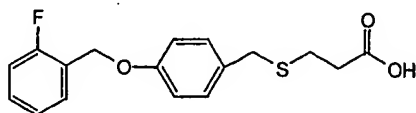
$^1\text{H}$  NMR (270 MHz,  $\text{CDCl}_3$ ): 1.2 (t, 3H); 2.6 (t, 2H); 3.2 (t, 2H); 3.8 (s, 3H); 4.1 (q,  
10 2H); 5.1 (s, 2H); 6.9-7.0 (m, 4H); 7.1-7.3 (m, 2H); 7.9 (d, 2H).

Step C: Preparation of 4-(4-(2-Methoxybenzyloxy)phenyl)-4-oxobutyric acid:

A solution of Ethyl 4-(4-(2-methoxybenzyloxy)phenyl)-4-oxobutyrate (Step B, 1.49 g,  
15 4.3 mmol) in abs ethanol (20 ml) was treated with 1N NaOH (6 ml). The reaction mixture was stirred at room temperature for 2 hours and then acidified with 1M HCl. The resulting white solid was filtered, washed with cold water and dried under vacuum to provide the title compound.

$^1\text{H}$  NMR (270 MHz,  $\text{CDCl}_3$ ;  $\text{CD}_3\text{OD}$ ): 2.6 (t, 2H); 3.2 (t, 2H); 3.8 (s, 3H); 5.1 (s, 2H);  
20 6.9-7.0 (m, 4H); 7.2-7.3 (m, 2H); 7.8 (d, 2H).

EXAMPLE 3: Synthesis of 3-[(4-(2-Fluorobenzyloxy)phenyl)-methylthio]propionic acid.



Step A: Preparation of 4-Hydroxybenzyl bromide:

To a stirred solution of  $\text{PBr}_3$  (1.38 g, 5.0 mmol) in dry THF (2 ml) at  $-5^{\circ}\text{C}$  was added a solution of dry pyridine (.201 ml) in dry THF (.4 ml). A solution of 4-Hydroxybenzyl  
30

alcohol (1.89 g, 15.2 mmol) in dry THF (23 ml) was added drop wise to the reaction mixture. The reaction mixture was allowed to stand at room temperature for 18 hours, then diluted with THF and filtered through celite pad. The filtrate was evaporated, the resulting semisolid was redissolved in dry toluene (16ml). The solution was maintained  
5 at  $-20^{\circ}\text{C}$  for 2 hours, and then filtered through celite pad to provide the title compound as a light yellow solution which was used without further purification.

Step B: Preparation of Ethyl 3-((4-hydroxyphenyl)-methylthio)propionate:

- 10 To a solution of NaH (60% dispersed in oil, .731 g, 21.7 mmol) in dry DMF (15 ml) was added Ethyl 3-mercaptopropionate (2.66 g, 19.8 mmol). When the evolution of hydrogen ceased, 4-Hydroxybenzyl bromide from Step A was added. The reaction mixture was stirred for 16 hours at room temperature, quenched with sat.  $\text{NH}_4\text{Cl}$  and concentrated in vacuo. The crude residue was taken in EtOAc and washed with water  
15 and brine. The aqueous layer was washed one more time with EtOAc. The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated. The purification was done by flash chromatography on silica gel column (dichloromethane: ethyl acetate, 95:5) to provide the title compound.
- 20  $^1\text{H}$  NMR (270 MHz,  $\text{CDCl}_3$ ): 1.2 (t, 3H); 2.4-2.6 (m, 4H); 3.6 (s, 2H); 4.1 (q, 2H); 6.7 (d, 2H); 7.2 (d, 2H).

Step C: Preparation of Ethyl 3-((4-(2-fluorobenzyloxy)phenyl)-methylthio)propionate:

- 25 To a solution of NaH (60% dispersed in oil, .054 g, 1.3 mmol) in dry DMF (10 ml) was added Ethyl 3-((4-hydroxyphenyl)-methylthio)propionate (Step B, 2.5 g, 1.0 mmol). When the evolution of hydrogen ceased, 2-Fluorobenzyl bromide (.263 g, 1.3 mmol) was added. The reaction mixture was stirred for 4 hours at room temperature, quenched with sat.  $\text{NH}_4\text{Cl}$ , and concentrated in vacuo. The crude residue was taken in EtOAc and  
30 washed twice with water and brine. The aqueous layer was washed one more time with EtOAc. The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated. The purification was done by flash chromatography on silica gel column (hex: ethyl acetate, 4:1) to provide the title compound.

$^1\text{H}$  NMR (270 MHz,  $\text{CDCl}_3$ ): 1.2 (t, 3H); 2.4-2.6 (m, 4H); 3.6 (s, 2H); 4.2 (q, 2H); 5.15 (s, 2H); 6.9 (d, 2H); 7.2-7.4 (m, 5H); 7.5 (t, 1H).

Step D: Preparation of 3-((4-(2-fluorobenzyloxy)phenyl)-methylthio)propionic acid:

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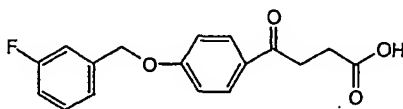
To a solution of Ethyl 3-((4-(2-fluorobenzyloxy)phenyl)-methylthio)propionate (Step C, .122 g, .35 mmol) in ethanol (5 ml) was added 1N NaOH (.5 ml) at room temperature. The reaction mixture was stirred for 3 hours, acidified with 1M HCl and concentrated in vacuo to give white solid which was purified by flash chromatography on silica gel column (chloroform: methanol, 92.5:7.5 spiked with acetic acid ) to provide the title compound as a white solid.

10

$^1\text{H}$  NMR (270 MHz,  $\text{CDCl}_3$ ): 2.4-2.6 (m, 4H); 3.7 (s, 2H); 5.1 (s, 2H); 6.9 (d, 2H); 7.2-7.4 (m, 5H); 7.5 (t, 1H).

15

EXAMPLE 4: Synthesis of 4-(4-(3-Fluorobenzyloxy)phenyl)-4-oxobutyrac acid



20

Step A: Preparation of 4-(3-Fluorobenzyloxy)acetophenone:

Using the method of Example 1, Step A, using 3-Fluorobenzyl bromide as the starting material, the title compound was obtained.

25

$^1\text{H}$  NMR (270 MHz,  $\text{CDCl}_3$ ): 2.5 (s, 3H); 5.1 (s, 2H); 7.0 (m, 3H); 7.2-7.3 (t, 2H); 7.4 (m, 1H); 7.9 (d, 2H).

Step B: Preparation of tert-Butyl 4-(4-(3-fluorobenzyloxy)phenyl)-4-oxobutyrac:

30

Using the method of Example 1, Step B, the title compound was obtained.

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 1.4 (s, 9H); 2.7 (t, 2H); 3.2 (t, 2H); 5.1 (s, 2H); 7.0 (m, 3H); 7.2 (t, 2H); 7.4 (m, 1H); 8.0 (d, 2H).

Step C: Preparation of 4-(4-(3-Fluorobenzoyloxy)phenyl)-4-oxobutyric acid:

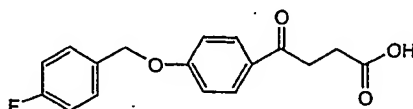
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Using the method of Example 1, Step C, the title compound was obtained.

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 2.8 (t, 2H); 3.2 (t, 2H); 5.1 (s, 2H); 6.9-7.1 (m, 3H); 7.2-7.3 (m, 2H); 7.4 (q, 1H); 7.9 (d, 2H).

10

EXAMPLE 5: Synthesis of 4-(4-(4-Fluorobenzoyloxy)phenyl)-4-oxobutyric acid



15

Step A: Preparation of 4-(4-Fluorobenzoyloxy)acetophenone:

Using the method of Example 1, Step A, using 4-Fluorobenzyl bromide as the starting material, the title compound was obtained.

20

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 2.5 (s, 3H); 5.1 (s, 2H); 7.0 (d, 2H); 7.1 (t, 2H); 7.4 (m, 2H); 7.9 (d, 2H).

25 Step B: Preparation of tert-Butyl 4-(4-(4-fluorobenzoyloxy)phenyl)-4-oxobutyrate:

Using the method of Example 1, Step B, the title compound was obtained

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 1.4 (s, 9H); 2.8 (t, 2H); 3.2 (t, 2H); 5.1 (s, 2H); 7.0 (m, 2H); 7.2 (t, 2H); 7.4 (m, 2H); 8.0 (d, 2H).

30

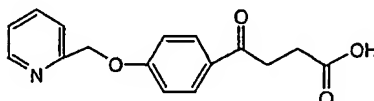
Step C: Preparation of 4-(4-(4-Fluorobenzoyloxy)phenyl)-4-oxobutyric acid:

Using the method of Example 1, Step C, the title compound was obtained.

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 2.8 (t, 2H); 3.2 (t, 2H); 5.1 (s, 2H); 6.9-7.1 (m, 2H); 7.2-7.3 (d, 2H); 7.4 (m, 2H); 7.9 (d, 2H).

5

EXAMPLE 6: Synthesis of 4-(4-((2-Pyridinyl)-methoxy)phenyl)-4-oxobutyrac acid



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Step A: Preparation of 4-((2-Pyridinyl)-methoxy)acetophenone:

A solution of 4-Hydroxyacetophenone (1.99 g, 14.6 mmol) in dry DMF (5 ml) was added at room temperature to a suspension of NaH (60% in oil, .604 g) in dry DMF (20 ml). When evolution of hydrogen ceased, 2-Picolyl chloride hydrochloride (2 g, 12.1 mmol) was added. The reaction mixture was stirred at room temperature for 16 hours, quenched with sat aq. NH<sub>4</sub>Cl and concentrated in vacuo. The crude residue was taken in EtOAc and washed with water and brine. The aqueous layer was washed twice with EtOAc. The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified by flash chromatography on silica gel column (hex: ethyl acetate, 1:1) to provide the title compound.

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 2.5 (s, 3H); 5.2 (s, 2H); 7.0 (d, 2H); 7.2 (m, 1H); 7.5 (d, 1H); 7.7 (t, 1H); 7.9 (d, 2H); 8.6 (s, 1H).

25

Step B: Preparation of tert-Butyl 4-(4-((2-pyridinyl)-methoxy)phenyl)-4-oxobutyratate:

To a stirred solution of 4-((2-Pyridinyl)-methoxy)acetophenone (Step A, .968 g, 3.6 mmol) in dry THF (16 ml) and DMPU (4 ml) was added a solution of lithium bis(trimethylsilyl)amide (1.0M, 5 ml) at -60°C under argon. After stirring for 10 minutes at -60°C, tert-Butyl bromoacetate (2.64 g, 13.5 mmol) was added rapidly. The

30

reaction mixture was stirred for an additional 10 minutes and then warmed to room temperature for 4 hours. The crude mixture was taken in EtOAc and washed with water and brine. The aqueous layer was extracted one more time with EtOAc. The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated and purified by flash chromatography on silica gel column (hex: ethyl acetate, 2:1) to provide the title compound.

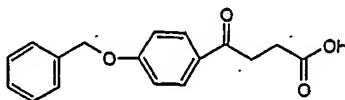
<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 1.4 (s, 9H); 2.7 (t, 2H); 3.2 (t, 2H); 5.3 (s, 2H); 7.0 (d, 2H); 7.2 (m, 1H); 7.5 (d, 1H); 7.7 (t, 1H); 7.9 (d, 2H); 8.6 (s, 1H).

Step C: Preparation of 4-(4-((2-Pyridinyl)-methoxy)phenyl)-4-oxobutyric acid:

A solution of tert-Butyl 4-(4-((2-pyridinyl)-methoxy)phenyl)-4-oxobutyrate (Step C, 1.27 g, 4.2 mmol) in dichloromethane (25 ml) was treated with trifluoroacetic acid (5 ml). The mixture was stirred at ambient temperature for 3 hours and concentrated in vacuo. The purification was done by flash chromatography on silica gel column (chloroform: methanol, 95:5 spiked with acetic acid) to provide the title compound as a white solid.

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>:CD<sub>3</sub>OD): 2.7 (t, 2H); 3.2 (t, 2H); 5.3 (s, 2H); 7.0 (d, 2H); 7.3 (m, 1H); 7.5 (d, 1H); 7.9 (m, 3H); 8.6 (s, 1H).

EXAMPLE 7: Synthesis of 4-(4-(Benzyloxy)phenyl)-4-oxobutyric acid



Step A: Preparation of 4-(Benzyloxy)acetophenone:

Using the method of Example 1, Step A, using Benzyl bromide as the starting material, the title compound was obtained.

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 2.5 (s, 3H); 5.1 (s, 2H); 7.0 (d, 2H); 7.3-7.5 (m, 5H); 7.9 (d, 2H).

Step B: Preparation of tert-Butyl 4-(4-(benzyloxy)phenyl)-4-oxobutyrates:

5

Using the method of Example 1, Step B, the title compound was obtained.

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 1.4 (s, 9H); 2.6 (t, 2H); 3.2 (t, 2H); 5.2 (s, 2H); 7.0 (d, 2H); 7.3-7.5 (m, 5H); 7.9 (d, 2H).

10

Step C: Preparation of 4-(4-(Benzyloxy)phenyl)-4-oxobutyric acid:

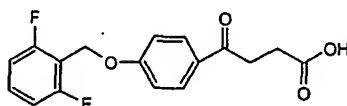
Using the method of Example 1, Step C, the title compound was obtained.

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 2.8 (t, 2H); 3.2 (t, 2H); 5.1 (s, 2H); 7.0 (d, 2H); 7.3-7.5 (m, 5H); 7.9 (d, 2H).

15

EXAMPLE 8: Synthesis of 4-(4-(2,6-Difluorobenzyloxy)phenyl)-4-oxobutyric acid

20



Step A: Preparation of 4-(2,6-Difluorobenzyloxy)acetophenone:

A solution of 4-Hydroxyacetophenone (3.61 g, 26.5 mmol) in dry DMF (5 ml) was added at room temperature to a suspension of NaH (60% in oil, 1.21 g) in dry DMF (40 ml). When evolution of hydrogen ceased, 2,6-Difluorobenzyl bromide (5 g, 24.1 mmol) was added drop wise. The reaction mixture was stirred at room temperature for 6 hours, quenched with sat aq. NH<sub>4</sub>Cl and concentrated in vacuo. The crude residue was taken in EtOAc and washed with water and brine. The aqueous layer was extracted one more time with EtOAc. The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified by flash chromatography on silica gel column (hex: ethyl acetate, 2:1) to provide the title compound.

30



<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 2.5 (s, 3H); 5.2 (s, 2H); 6.9-7.0 (m, 4H); 7.3-7.4 (m, 1H); 7.9 (d, 2H).

Step B: Preparation of tert-Butyl 4-(4-(2,6-difluorobenzyloxy)phenyl)-4-oxobutyrates:

5 To a stirred solution of 4-(2,6-Difluorobenzyloxy)acetophenone (Step A, .6 g, 22.8 mmol) in dry THF (60 ml) and DMPU (12 ml) was added a solution of lithium bis(trimethylsilyl)amide (1.0M, 30 ml) at -60°C under argon. After stirring for 10 minutes at -60°C, tert-Butyl bromoacetate (8.97 g, 46 mmol) was added rapidly. The  
10 reaction mixture was stirred for an additional 10 minutes and then warmed to room temperature for 4 hours. The crude mixture was taken in EtOAc and washed with water and brine. The aqueous layer was extracted one more time with EtOAc. The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated and purified by flash chromatography on a silica gel column (hex: ethyl acetate, 2:1) to provide the title  
15 compound as a white solid.

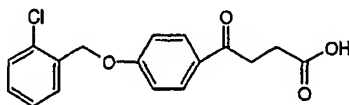
<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 1.4 (s, 9H); 2.6 (t, 2H); 3.2 (t, 2H); 5.2 (s, 2H); 6.9-7.0 (m, 4H); 7.3-7.4 (m, 1H); 7.9 (d, 2H).

20 Step C: Preparation of 4-(4-(2,6-Difluorobenzyloxy)phenyl)-4-oxobutyric acid:

A solution of tert-Butyl 4-(4-(2,6-difluorobenzyloxy)phenyl)-4-oxobutyrates (Step B, 4.76 g, 12.6 mmol) in dichloromethane (40 ml) was treated with trifluoroacetic acid (20 ml). The mixture was stirred at ambient temperature for 3 hours and concentrated in  
25 vacuo. The purification was done by flash chromatography on silica gel column (chloroform: methanol, 95:5 spiked with acetic acid) to provide the title compound as a white powder.

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 2.8 (t, 2H); 3.2 (t, 2H); 5.2 (s, 2H); 6.9-7.0 (m, 4H); 7.4  
30 (m, 1H); 7.9 (d, 2H).

## EXAMPLE 9: Synthesis of 4-(4-(2-Chlorobenzoyloxy)phenyl)-4-oxobutyric acid



5.

Step A: Preparation of 4-(2-Chlorobenzoyloxy)acetophenone:

Using the method of Example 1, Step A, using 2-Chlorobenzyl bromide as the starting material, the title compound was obtained.

10

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 2.5 (s, 3H); 5.2 (s, 2H); 7.0 (d, 2H); 7.2-7.5 (m, 4H); 7.9 (d, 2H).

Step B: Preparation of tert-Butyl 4-(4-(2-chlorobenzoyloxy)phenyl)-4-oxobutyrate:

15

Using the method of Example 1, Step B, the title compound was obtained.

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 1.4 (s, 9H); 2.6 (t, 2H); 3.2 (t, 2H); 5.2 (s, 2H); 7.0 (d, 2H); 7.2-7.5 (m, 4H); 7.9 (d, 2H).

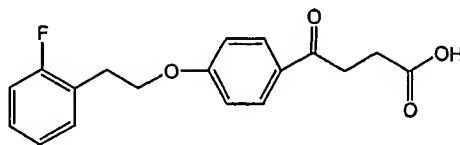
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Step C: Preparation of 4-(4-(2-Chlorobenzoyloxy)phenyl)-4-oxobutyric acid:

Using the method of Example 1, Step C, the title compound was obtained.

25 <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>:CD<sub>3</sub>OD): 2.6 (t, 2H); 3.2 (t, 2H); 5.2 (s, 2H); 7.0 (d, 2H); 7.2 (m, 2H); 7.3 (m, 1H); 7.4 (m, 1H); 7.9 (d, 2H).

EXAMPLE 10: Synthesis of 4-(4-(2-(2-Fluorophenyl)ethoxy)phenyl)-4-oxobutyric acid



5

Step A: Preparation of 4-(2-(2-fluorophenyl)ethoxy)acetophenone:

Using the method of Example 2, Step A, using 2-Fluorophenethyl alcohol as the starting material, the title compound was obtained.

10

$^1\text{H}$  NMR (270 MHz,  $\text{CDCl}_3$ ): 2.3 (s, 3H); 2.9 (t, 2H); 4.2 (t, 2H); 6.9 (d, 2H); 7.1 (m, 2H); 7.3 (m, 2H); 7.9 (d, 2H).

Step B: Preparation of tert-Butyl 4-(4-(2-(2-fluorophenyl)ethoxy)phenyl)-4-oxobutyrate:

15

Using the method of Example 2, Step B, using tert-Butyl bromoacetate as the starting material, the title compound was obtained.

20  $^1\text{H}$  NMR (270 MHz,  $\text{CDCl}_3$ ): 1.4 (s, 9H); 2.6 (t, 2H); 3.2 (m, 4H); 4.2 (t, 2H); 6.9 (d, 2H); 7.1 (m, 2H); 7.3 (t, 2H); 7.9 (d, 2H).

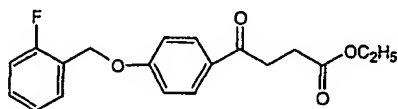
Step C: Preparation of 4-(4-(2-(2-Fluorophenyl)ethoxy)phenyl)-4-oxobutyric acid:

25 A solution of tert-Butyl 4-(4-(2-(2-Fluorophenyl)ethoxy)phenyl)-4-oxobutyrate (Step 2, 1.2 g, 3.2 mmol) in dichloromethane (25 ml) was treated with trifluoroacetic acid (10 ml). The reaction mixture was stirred at ambient temperature for 4 hours and concentrated in vacuo. The purification was done by flash chromatography on silica gel column (chloroform: methanol, 95:5 spiked with acetic acid) to provide the title  
30 compound as a white solid.

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 2.8 (t, 2H); 3.3 (t, 2H); 4.2 (t, 2H); 6.9 (d, 2H); 7.1 (m, 2H); 7.3 (t, 2H); 7.9 (d, 2H).

EXAMPLE 11: Synthesis of Ethyl 4-(4-(2-Fluorobenzoyloxy)phenyl)-4-oxobutyrates

5



Step A: Preparation of 4-(4-(2-Fluorobenzoyloxy)acetophenone:

10

Using the method of Example 1, Step A, the title compound was obtained.

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 2.5 (s, 3H); 5.2 (s, 2H); 6.9-7.1 (m, 4H); 7.2-7.3 (m, 1H); 7.4 (t, 1H); 7.9 (d, 2H).

15

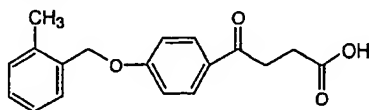
Step B: Preparation of Ethyl 4-(4-(2-fluorobenzoyloxy)phenyl)-4-oxobutyrates:

To a stirred solution of 4-(2-Fluorobenzoyloxy)acetophenone (7.26 g, 29.7 mmol) in dry THF (80 ml) and DMPU (16 ml) was added a solution of lithium

20 bis(trimethylsilyl)amide (1.0M, 35 ml) at -60°C under argon. After stirring for 10 minutes at -60°C, Ethyl bromoacetate (10.12 g, 60.5 mmol) was added rapidly. The reaction mixture was stirred for an additional 10 minutes and then warmed to room temperature for 4 hours. The crude mixture was taken in EtOAc and washed with water and brine. The aqueous layer was extracted one more time with EtOAc. The combined  
25 organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated and purified by flash chromatography on a silica gel column (hex: ethyl acetate, 4:1) to provide the title compound as a white powder.

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 1.2 (t, 3H); 2.7 (t, 2H); 3.2 (t, 2H); 4.2 (q, 2H); 5.1 (s, 30 2H); 6.9 (d, 2H); 7.2 (m, 2H); 7.4 (m, 1H); 7.5 (m, 1H); 7.9 (d, 2H).

## EXAMPLE 12: Synthesis of 4-(4-(2-Methylbenzyloxy)phenyl)-4-oxobutyrlic acid



## Step A: Preparation of 4-(2-Methylbenzyloxy)acetophenone:

5

Using the method of Example 1, Step A, using 2-Methylbenzyl bromide as the starting material, the title compound was obtained.

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 2.4 (s, 3H); 2.5 (s, 3H); 5.2 (s, 2H); 6.9 (d, 2H); 7.2-7.3 (m, 3H); 7.4 (m, 1H); 7.9 (d, 2H).

10

## Step B: Preparation of tert-Butyl 4-(4-(2-methylbenzyloxy)phenyl)-4-oxobutyrate:

Using the method of Example 1, Step B, the title compound was obtained.

15

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 1.5 (s, 9H); 2.4 (s, 3H); 2.6 (t, 2H); 3.2 (t, 2H); 5.2 (s, 2H); 6.9 (d, 2H); 7.2-7.3 (m, 3H); 7.4 (m, 1H); 7.9 (d, 2H).

## Step C: Preparation of 4-(4-(2-Methylbenzyloxy)phenyl)-4-oxobutyrlic acid:

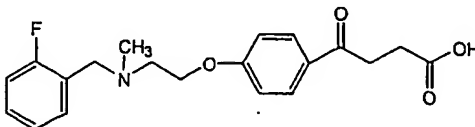
20

Using the method of Example 1, Step C, the title compound was obtained.

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 2.4 (s, 3H); 2.8 (t, 2H); 3.2 (t, 2H); 5.1 (s, 2H); 6.9 (d, 2H); 7.2-7.3 (m, 3H); 7.4 (m, 1H); 7.9 (d, 2H).

25

## EXAMPLE 13: Synthesis of 4-[4-(2-(N-(2-fluorobenzyl)-N-methylamino)ethoxy)phenyl]-4-oxobutyrlic acid



30

Step A: Preparation of 2-Fluorobenzyl methanesulfonate:

To a solution of 2-Fluorobenzyl alcohol (10 g, 79.28 mmol) in dry dichloromethane (200 ml) was added triethylamine (12.03 g, 118.9 mmol) under argon at room temperature. Methanesulfonyl chloride (10.71 g, 93.5 mmol) was added to the above reaction mixture at 0°C, and stirring was continued for another 3 hours. Water (100 ml) was added to the reaction mixture and the mixture was extracted twice with dichloromethane. The combined organic layers were washed with water and brine. The reaction mixture was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give the title compound as an yellow oil which was used without further purification.

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 1.3 (t, 3H); 2.4-2.6 (m, 4H); 5.25 (s, 2H); 6.9-7.5 (m, 4H).

Step B: Preparation of 2-(N-(2-fluorobenzyl)-N-methylamino)-ethanol:

A mix of 2-Fluorobenzyl methanesulfonate (Step A, 5 g, 24.5 mmol) and 2-(Methylamino)-ethanol (18.4 g, 244.9 mmol) was heated under argon at 120°C with stirring for 7 hours. The mixture was cooled to room temperature and concentrated. The crude residue was purified by flash chromatography on silica gel column (chloroform: methanol, 90:10 spiked with triethylamine) to provide the title compound.

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 2.3 (s, 3H); 2.6 (m, 2H); 3.6 (m, 4H); 6.9-7.5 (m, 4H).

Step C: Preparation of 2-(N-(2-fluorobenzyl)-N-methylamino)-ethyl chloride:

To a solution of 2-(N-(2-fluorobenzyl)-N-methylamino)-ethanol (Step B, 7.51 g, 41 mmol) in dry toluene (50 ml) was added thionyl chloride (16 ml). The reaction mixture was stirred at room temperature for 16 hours and concentrated. The crude mixture was diluted with chloroform and washed with aq NaHCO<sub>3</sub>, water and brine. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to provide the title compound which was used without further purification.

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 2.3 (s, 3H); 2.8 (t, 2H); 3.6 (t, 2H); 3.7 (s, 2H); 7.0-7.15 (m, 2H); 7.25 (m, 1H), 7.4 (t, 1H).

Step D: Preparation of 4-(2-(N-(2-fluorobenzyl)-N-methylamino)ethoxy)acetophenone:

To a solution of 2-(N-(2-fluorobenzyl)-N-methylamino)-ethyl chloride (Step C, 7.48 g, 37 mmol) and 4-Hydroxyacetophenone (10.07 g, 74 mmol) in dry DMF (10 ml) was added  $K_2CO_3$  (7.77 g, 56.2 mmol). The mixture was heated at 80°C for 6 hours, cooled, quenched with water and extracted twice with EtOAc. The combined organic layers were dried over  $Na_2SO_4$ , filtered and concentrated. The crude residue was purified by flash chromatography on silica gel column (hex: ethyl acetate, 2:1) to provide the title compound as a light yellow oil.

<sup>1</sup>H NMR (270 MHz,  $CDCl_3$ ): 2.35 (s, 3H); 2.4 (s, 3H); 2.8 (t, 2H); 3.7 (s, 2H); 4.2 (t, 2H); 6.9 (d, 2H); 7.0-7.15(m, 2H); 7.25 (m, 1H), 7.4 (t, 1H); 7.9 (d, 2H).

Step E: Preparation of tert-Butyl 4-[4-(2-(N-(2-fluorobenzyl)-N-methylamino)ethoxy)phenyl]-4-oxobutyrates:

Lithium bis(trimethylsilyl)amide (1.0M, 20 ml) was added slowly over 10 minutes to a stirred solution of 4-(2-(N-(2-fluorobenzyl)-N-methylamino)ethoxy)acetophenone (Step D, 4.91 g, 16.3 mmol) in dry THF (60 ml) and DMPU (15 ml) at -65°C under argon. After 15 minutes of stirring, tert-Butyl bromoacetate (6.35 g, 32.6 mmol) was added rapidly. The stirring continued for an additional 10 minutes at -65°C and then reaction was warmed to room temperature for 2 hours, quenched with water and extracted twice with EtOAc. The combined organic layers were purified by flash chromatography on silica gel column (hex: ethyl acetate, 1:1) to provide the title compound.

<sup>1</sup>H NMR (270 MHz,  $CDCl_3$ ): 1.5 (s, 9H); 2.4 (s, 3H); 2.6 (t, 2H); 2.8 (t, 2H); 3.2 (t, 2H); 3.7 (br, 2H); 4.2 (br, 2H); 6.9 (d, 2H); 7.0-7.15(m, 2H); 7.25 (m, 1H), 7.4 (t, 1H); 7.9 (d, 2H).

Step F: Preparation of 4-[4-(2-(N-(2-fluorobenzyl)-N-methylamino)ethoxy)phenyl]-4-oxobutyric acid:

A solution of tert-Butyl 4-[4-(2-(N-(2-fluorobenzyl)-N-methylamine)ethoxy)phenyl]-4-oxobutyrate (Step E, 2.23 g, 5.3 mol) in dichloromethane (20 ml) was treated with

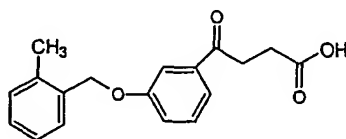
trifluoroacetic acid (10 ml). The reaction mixture was stirred at ambient temperature for 2 hours, and concentrated in vacuo. The purification was done by flash chromatography on silica gel column (chloroform: methanol, 92.5:7.5-90:10 spiked with acetic acid) to provide the title compound.

5

$^1\text{H}$  NMR (270 MHz,  $\text{CDCl}_3:\text{CD}_3\text{OD}$ ): 2.5 (t, 2H); 2.6 (s, 3H); 3.0 (t, 2H); 3.4 (t, 2H); 4.2-4.5 (m, 4H); 6.9 (d, 2H); 7.0-7.15 (m, 2H); 7.3 (m, 1H), 7.5 (t, 1H); 7.9 (d, 2H).

EXAMPLE 14: Synthesis of 4-(3-(2-Methylbenzyloxy)phenyl)-4-oxobutyrac acid

10



Step A: Preparation of 3-(2-Methylbenzyloxy)acetophenone:

15 Using the method of Example 12, Step A, using 3-Hydroxyacetophenone as the starting material, the title compound was obtained.

$^1\text{H}$  NMR (270 MHz,  $\text{CDCl}_3$ ): 2.3 (s, 3H); 2.5 (s, 3H); 5.1 (s, 2H); 7.2-7.3 (m, 4H); 7.4 (m, 2H); 7.6 (m, 2H).

20 Step B: Preparation of tert-Butyl 4-(3-(2-methylbenzyloxy)phenyl)-4-oxobutyracate:

Using the method of Example 1, Step B, the title compound was obtained.

25  $^1\text{H}$  NMR (270 MHz,  $\text{CDCl}_3$ ): 1.5 (s, 9H); 2.4 (s, 3H); 2.6 (t, 2H); 3.2 (t, 2H); 5.2 (s, 2H); 7.2-7.3 (m, 4H); 7.4 (m, 2H); 7.6 (m, 2H).

Step C: Preparation of 4-(3-(2-Methylbenzyloxy)phenyl)-4-oxobutyrac acid:

Using the method of Example 1, Step C, the title compound was obtained

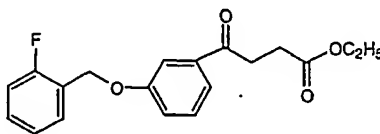
30



<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 2.4 (s, 3H); 2.8 (t, 2H); 3.3 (t, 2H); 5.1 (s, 2H); 7.2-7.3 (m, 4H); 7.4 (m, 2H); 7.6 (m, 2H).

EXAMPLE 15: Synthesis of Ethyl 4-(3-(2-fluorobenzoyloxy)phenyl)-4-oxobutyrates

5



Step A: Preparation of 3-(2-Fluorobenzoyloxy)acetophenone:

- 10 Using the method of Example 1, Step A, using 3-Hydroxyacetophenone as the starting material, the title compound was obtained.

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 2.5 (s, 3H); 5.2 (s, 2H); 7.1 (m, 4H); 7.3 (m, 2H); 7.6 (m, 2H).

15

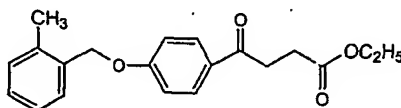
Step B: Preparation of Ethyl 4-(3-(2-fluorobenzoyloxy)phenyl)-4-oxobutyrates:

Using the method of Example 11, Step B, the title compound was obtained.

- 20 <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 1.3 (s, 9H); 2.8 (t, 2H); 3.3 (t, 2H); 5.1 (s, 2H); 7.1 (t, 2H); 7.2 (d, 2H); 7.4 (m, 1H); 7.5 (t, 1H); 7.6 (d, 2H).

EXAMPLE 16: Synthesis of Ethyl 4-(4-(2-methylbenzyloxy)phenyl)-4-oxobutyrates

25



Step A: Preparation of 4-(2-Methylbenzyloxy)acetophenone:

- 30 Using the method of Example 12, Step A, the title compound was obtained.

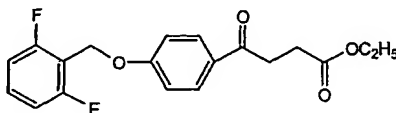
<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 2.4 (s, 3H); 2.5 (s, 3H); 5.2 (s, 2H); 6.9 (d, 2H); 7.2-7.3 (m, 3H); 7.4 (m, 1H); 8.0 (d, 2H).

5 Step B: Preparation of Ethyl 4-(4-(2-methylbenzyloxy)phenyl)-4-oxobutyrates:

Using the method of Example 11, Step B, the title compound was obtained.

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 1.2 (t, 3H); 2.4 (s, 3H); 2.7 (t, 2H); 3.2 (t, 2H); 4.2 (q, 10 2H); 5.1 (s, 2H); 7.0 (d, 2H); 7.2-7.3 (m, 3H); 7.4 (m, 1H); 8.0 (d, 2H).

EXAMPLE 17: Synthesis of Ethyl 4-(4-(2,6-difluorobenzyloxy)phenyl)-4-oxobutyrates



15

Step A: Preparation of 4-(2,6-Difluorobenzyloxy)acetophenone:

Using the method of Example 8, Step A, the title compound was obtained

20 <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 2.5 (s, 3H); 5.2 (s, 2H); 6.9-7.0 (m, 4H); 7.3-7.4 (m, 1H); 7.9 (d, 2H).

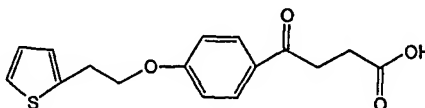
Step B: Preparation of Ethyl 4-(4-(2,6-Difluorobenzyloxy)phenyl)-4-oxobutyrates:

25 To a stirred solution of 4-(2,6-Difluorobenzyloxy)acetophenone (Step A, ..6 g, 22.8 mmol) in dry THF (60 ml) and DMPU (12 ml) was added a solution of lithium bis(trimethylsilyl)amide (1.0M, 30 ml) at -60°C under argon. After stirring for 10 minutes at -60°C, Ethyl bromoacetate (7.61 g, 45.6 mmol) was added rapidly. The reaction mixture was stirred for an additional 10 minutes and then warmed to room  
30 temperature for 4 hours. The crude mixture was taken in EtOAc and washed with water and brine. The aqueous layer was extracted one more time with EtOAc. The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated and purified by flash

chromatography on silica gel column (hex: ethyl acetate, 4:1) to provide the title compound as a white solid.

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 1.3 (t, 3H); 2.8 (t, 3H); 3.2 (t, 2H); 4.1 (q, 2H); 5.2 (s, 2H); 6.9-7.0 (m, 4H); 7.3-7.4 (m, 1H); 7.9 (d, 2H).

EXAMPLE 18: Synthesis of 4-(4-(2-(2-Thienyl)ethoxy)phenyl)-4-oxobutyric acid



Step A: Preparation of 4-(2-(2-Thienyl)ethoxy)acetophenone:

Using the method of Example 2, Step A, using 2-(2-Thienyl)ethanol as the starting material and purification by flash chromatography on silica gel column (hex: ethylacetate, 3:1), the title compound was obtained.

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 2.5 (s, 3H); 3.3 (t, 2H); 4.2 (t, 2H); 6.9-7.1 (m, 4H); 7.2 (d, 1H); 7.9 (d, 2H).

Step B: Preparation of Ethyl 4-(4-(2-(2-thienyl)ethoxy)phenyl)-4-oxobutyrate:

Using the method of Example 2, Step B, the title compound was obtained.

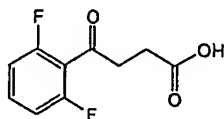
<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 1.3 (t, 3H); 2.8 (t, 2H); 3.3 (m, 4H); 4.1 (q, 2H); 4.2 (t, 2H); 6.9-7.1 (m, 4H); 7.2 (d, 1H); 7.9 (d, 2H).

Step C: Preparation of 4-(4-(2-(2-Thienyl)ethoxy)phenyl)-4-oxobutyric acid:

Using the method of Example 2, Step C, the title compound was obtained

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 2.8 (t, 2H); 3.3 (m, 4H); 4.2 (t, 2H); 6.9-7.1 (m, 4H); 7.2 (d, 1H); 7.9 (d, 2H).

## EXAMPLE 19: Synthesis of 4-(2,6-Difluorophenyl)-4-oxobutyric acid



## 5 Step A: Preparation of tert-Butyl 4-(2,6-difluorophenyl)-4-oxobutyrate:

To a stirred solution of 2,6-Difluoroacetophenone (5 g, 32 mmol) in dry THF (40 ml) and DMPU (8 ml) was added a solution of lithium bis(trimethylsilyl)amide (1.0M, 45 ml) at  $-60^{\circ}\text{C}$  under argon. After stirring for 10 minutes at  $-60^{\circ}\text{C}$ , tert-Butyl  
10 bromoacetate (6.99 g, 35.8 mmol) was added rapidly. The reaction mixture was stirred for an additional 10 minutes and then warmed to room temperature for 4 hours. The crude mixture was taken in EtOAc and washed with water and brine. The aqueous layer was extracted one more time with EtOAc. The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ , filtered, concentrated and purified by flash chromatography on a silica gel  
15 column (hex: ethyl acetate, 2:1) to provide the title compound.

$^1\text{H}$  NMR (270 MHz,  $\text{CDCl}_3$ ): 1.4 (s, 9H); 2.8 (t, 2H); 3.2 (t, 2H); 6.9-7.0 (m, 2H); 7.4 (m, 1H).

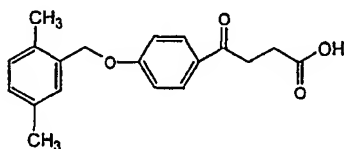
## 20 Step B: Preparation of Compound AS:

A solution of tert-Butyl 4-(2,6-difluorophenyl)-4-oxobutyrate (Step A, 9.52 g, 35.2 mmol) in dichloromethane (30 ml) was treated with trifluoroacetic acid (20 ml). The mixture was stirred at ambient temperature for 3 hours and concentrated. The  
25 purification was done by flash chromatography on silica gel column (chloroform: methanol, 95:5 spiked with acetic acid) to provide the title compound as a white solid.

$^1\text{H}$  NMR (270 MHz,  $\text{CDCl}_3$ ): 2.8 (t, 2H); 3.2 (t, 2H); 6.9-7.0 (m, 2H); 7.4 (m, 1H).

30

## EXAMPLE 20: Synthesis of 4-(4-(2,5-Dimethylbenzyloxy)phenyl)-4-oxobutyrlic acid



## 5 Step A: Preparation of 4-(2,5-Dimethylbenzyloxy)acetophenone:

Using the method of Example 8, Step A, using 2,5-Dimethylbenzyl chloride as the starting material, the title compound was obtained.

10 <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 2.3 (s, 3H); 2.5 (s, 3H); 5.1 (s, 2H); 6.9-7.2 (m, 5H); 7.9 (d, 2H).

## Step B: Preparation of Ethyl 4-(4-(2,5-dimethylbenzyloxy)phenyl)-4-oxobutyrate:

15 Using the method of Example 17, Step B, the title compound was obtained.

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 1.2 (s, 3H); 2.3 (s, 6H); 2.8(t, 2H); 3.2 (t, 2H); 4.4 (q, 2H); 5.1 (s, 2H); 7.0 (d, 2H); 7.2-7.3 (m, 3H); 7.9 (d, 2H).

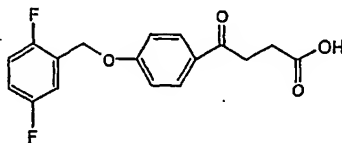
## 20 Step C: Preparation of 4-(4-(2,5-Dimethylbenzyloxy)phenyl)-4-oxobutyrlic acid:

To a solution of Ethyl 4-(4-(2,5-dimethylbenzyloxy)phenyl)-4-oxobutyrate (Step B, 2.62 g, 7.7 mmol) in abs ethanol (30 ml) was added 1N NaOH (10 ml) at room temperature. The reaction mixture was stirred for 3 hours and then acidified with 1M  
25 HCl. The occurring white precipitate was filtered, washed with water and dried under vacuum to provide the title compound as a white solid.

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 2.3 (s, 6H); 2.8(t, 2H); 3.2 (t, 2H); 5.1 (s, 2H); 7.0 (d, 2H); 7.2-7.3 (m, 3H); 8.0 (d, 2H).

30

## EXAMPLE 21: Synthesis of 4-(4-(2,5-Difluorobenzyloxy)phenyl)-4-oxobutyrlic acid



## 5 Step A: Preparation of 4-(2,5-Difluorobenzyloxy)acetophenone:

Using the method of Example 8, Step A, using 2,5-Difluorobenzyl bromide as the starting material, the title compound was obtained.

10 <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 2.5 (s, 3H); 5.1 (s, 2H); 6.9-7.0 (m, 3H); 7.2 (m, 2H); 8.0 (d, 2H).

## Step B: Preparation of Ethyl 4-(4-(2,5-difluorobenzyloxy)phenyl)-4-oxobutyrate:

15 Using the method of Example 17, Step B, the title compound was obtained.

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 1.2 (s, 3H); 2.8 (t, 2H); 3.2 (t, 2H); 4.4 (q, 2H); 5.1 (s, 2H); 6.9-7.0 (m, 3H); 7.2 (m, 2H); 8.0 (d, 2H).

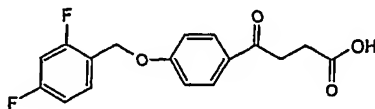
## 20 Step C: Preparation of 4-(4-(2,5-Difluorobenzyloxy)phenyl)-4-oxobutyrlic acid:

To a solution of Ethyl 4-(4-(2,5-Difluorobenzyloxy)phenyl)-4-oxobutyrate (Step B, 16.51 g, 47.4 mmol) in abs ethanol (100 ml) was added 1N NaOH (40 ml) at room temperature. The reaction mixture was stirred for 3 hours, acidified with 1M HCl and  
25 concentrated in vacuo. The crude mixture was taken in chloroform and washed with water. The aqueous layer was washed one more time with chloroform. The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The purification was done by flash chromatography on silica gel column (chloroform: methanol, 95:5 spiked with acetic acid) to provide the title compound as a white solid.

30

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 2.8 (t, 2H); 3.3 (t, 2H); 5.1 (s, 2H); 6.9-7.0 (m, 3H); 7.2 (m, 2H); 8.0 (d, 2H).

EXAMPLE 22: Synthesis of 4-(4-(2,4-Difluorobenzoyloxy)phenyl)-4-oxobutyric acid



Step A: Preparation of 4-(2,4-Difluorobenzoyloxy)acetophenone:

Using the method of Example 8, Step A, using 2,4-Difluorobenzyl bromide as the starting material, the title compound was obtained.

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 2.5(s, 3H); 5.1 (s, 2H); 6.9-7.0 (m, 2H); 7.1 (d, 2H); 7.4 (m, 1H); 8.0 (d, 2H).

Step B: Preparation of Ethyl 4-(4-(2,4-difluorobenzoyloxy)phenyl)-4-oxobutyrate:

Using the method of Example 17, Step B, the title compound was obtained.

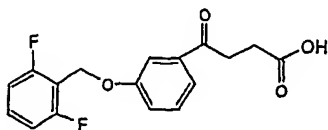
<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 1.2 (s, 3H); 2.8 (t, 2H); 3.2 (t, 2H); 4.4 (q, 2H); 5.1 (s, 2H); 6.9-7.0 (m, 2H); 7.1 (d, 2H); 7.4 (m, 1H); 8.0 (d, 2H).

Step C: Preparation of 4-(4-(2,4-Difluorobenzoyloxy)phenyl)-4-oxobutyric acid:

Using the method of Example 21, Step C, the title compound was obtained.

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 2.8 (t, 2H); 3.2 (t, 2H); 5.1 (s, 2H); 6.9-7.0 (m, 2H); 7.1 (d, 2H); 7.4 (m, 1H); 8.0 (d, 2H).

## EXAMPLE 23: Synthesis of 4-(3-(2,6-Difluorobenzoyloxy)phenyl)-4-oxobutyric acid



Step A: Preparation of 3-(2,6-Difluorobenzoyloxy)acetophenone:

5

Using the method of Example 8, Step A, using 3-Hydroxyacetophenone as the starting material, the title compound was obtained.

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 2.5 (s, 3H); 5.2 (s, 2H); 6.9-7.0 (m, 2H); 7.2 (m, 1H); 7.4 (m, 2H); 7.9 (d, 2H).

10

Step B: Preparation of Ethyl 4-(3-(2,6-difluorobenzoyloxy)phenyl)-4-oxobutyrate:

Using the method of Example 17, Step B, the title compound was obtained.

15

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 1.2 (s, 3H); 2.8(t, 2H); 3.2 (t, 2H); 4.4(q, 2H); 5.1 (s, 2H); 6.9-7.0 (m, 2H); 7.2 (m, 1H); 7.4 (m, 2H); 7.9 (d, 2H).

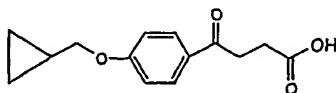
20 Step C: Preparation of 4-(3-(2,6-difluorobenzoyloxy)phenyl)-4-oxobutyric acid:

Using the method of Example 21, Step C, the title compound was obtained.

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 2.8(t, 2H); 3.2 (t, 2H); 5.1 (s, 2H); 6.9-7.0 (m, 2H); 7.2 (m, 1H); 7.4 (m, 2H); 7.9 (d, 2H).

25

## EXAMPLE 24: Synthesis of 4-(4-((Cyclopropyl) methoxy)phenyl)-4-oxobutyric acid



30



Step A: Preparation of 4-((Cyclopropyl)-methoxy)acetophenone:

Using the method of Example 8, Step A, using Cyclopropylmethyl bromide as the starting material, the title compound was obtained.

5

$^1\text{H}$  NMR (270 MHz,  $\text{CDCl}_3$ ): .4 (m, 2H); .6 (m, 2H); 1.2 (m, 1H); 2.5 (s, 3H); 3.8 (d, 2H); 6.9 (d, 2H); 7.9 (d, 2H).

Step B: Preparation of tert-Butyl 4-(4-((cyclopropyl)-methoxy)phenyl)-4-oxobutylate:

10

Using the method of Example 8, Step B, the title compound was obtained.

$^1\text{H}$  NMR (270 MHz,  $\text{CDCl}_3$ ): .4 (m, 2H); .6 (m, 2H); 1.2 (m, 1H); 1.4 (s, 9H); 2.6 (t, 2H); 3.2 (t, 2H); 3.8 (d, 2H); 6.9 (d, 2H); 7.9 (d, 2H).

15

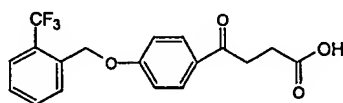
Step C: Preparation of 4-(4-((Cyclopropyl)-methoxy)phenyl)-4-oxobutyric acid:

Using the method of Example 8, Step C, the title compound was obtained.

20  $^1\text{H}$  NMR (270 MHz,  $\text{CDCl}_3$ ): .4 (m, 2H); .6 (m, 2H); 1.2 (m, 1H); 2.8 (t, 2H); 3.2 (t, 2H); 3.8 (d, 2H); 6.9 (d, 2H); 7.9 (d, 2H).

EXAMPLE 25: Synthesis of 4-(4-(2-Trifluoromethylbenzyloxy)phenyl)-4-oxobutyric acid

25



Step A: Preparation of 4-(2-Trifluoromethylbenzyloxy)acetophenone:

30 Using the method of Example 8, Step A, using 2-(Trifluoromethyl)benzyl bromide as the starting material, the title compound was obtained.

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 2.5 (s, 3H); 5.3 (s, 2H); 6.9 (d, 2H); 7.4 (t, 1H); 7.6 (t, 1H); 7.7 (d, 2H); 7.9 (d, 2H).

Step B: Preparation of tert-Butyl 4-(4-(2-trifluoromethylbenzyloxy)phenyl)-4-oxobutylate:

Using the method of Example 8, Step B, the title compound was obtained.

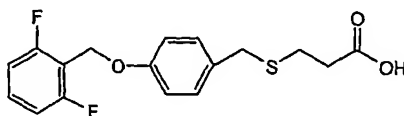
<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 1.4 (s, 9H); 2.7 (t, 2H); 3.2 (t, 2H); 5.3 (s, 2H); 6.9 (d, 2H); 7.4 (t, 1H); 7.6 (t, 1H); 7.7 (d, 2H); 7.9 (d, 2H).

Step C: Preparation of 4-(4-(2-Trifluoromethylbenzyloxy)phenyl)-4-oxobutyric acid:

Using the method of Example 8, Step C, the title compound was obtained.

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 2.8 (t, 2H); 3.2 (t, 2H); 5.3 (s, 2H); 6.9 (d, 2H); 7.4 (t, 1H); 7.6 (t, 1H); 7.7 (t, 2H); 7.9 (d, 2H).

EXAMPLE 26: Synthesis of 3-[(4-(2,6-Difluorobenzyloxy)phenyl)-methylthio]propionic acid



Step A: Preparation of 4-Hydroxybenzyl bromide:

Using the method of Example 3, Step A, the title compound was obtained which was used without further purification.

Step B: Preparation of Ethyl 3-[(4-hydroxyphenyl)-methylthio]propionate:

Using the method of Example 3, Step B, the title compound was obtained.

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 1.2 (t, 3H); 2.4-2.6 (m, 4H); 3.6 (s, 2H); 4.1 (q, 2H); 6.7 (d, 2H); 7.2 (d, 2H).

Step C: Preparation of Ethyl 3-[(4-(2,6-difluorobenzyloxy)phenyl)

5 methylthio]propionate:

Using the method of Example 3, Step C, using 2,6-Difluorobenzyl bromide as the starting material, the title compound was obtained.

10 <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 1.2 (t, 3H); 2.4-2.6 (m, 4H); 3.6 (s, 2H); 4.2 (q, 2H); 5.15 (s, 2H); 6.9 (d, 4H); 7.2-7.4 (m, 3H).

Step D: Preparation of 3-[(4-(2,6-Difluorobenzyloxy)phenyl)-methylthio]propionic acid:

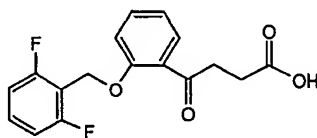
15

Using the method of Example 3, Step D, the title compound was obtained.

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 2.5-2.6 (m, 4H); 3.7 (s, 2H); 5.1 (s, 2H); 6.9-7.0 (m, 4H); 7.2-7.4 (m, 3H).

20

EXAMPLE 27: Synthesis of 4-(2-(2,6-Difluorobenzyloxy)phenyl)-4-oxobutyrac acid



25 Step A: Preparation of 2-(2,6-Difluorobenzyloxy)acetophenone:

Using the method of Example 8, Step A, using 2-Hydroxyacetophenone as the starting material, the title compound was obtained.

30 <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 2.5 (s, 3H); 5.2 (s, 2H); 6.9-7.0 (m, 3H); 7.1 (d, 1H); 7.4 (m, 1H); 7.5 (t, 1H); 7.8 (d, 1H).

Step B: Preparation of Ethyl 4-(2-(2,6-difluorobenzoyloxy)phenyl)-4-oxobutylate:

Using the method of Example 17, Step B, the title compound was obtained.

5  $^1\text{H}$  NMR (270 MHz,  $\text{CDCl}_3$ ): 1.2 (s, 3H); 2.6 (t, 2H); 3.2 (t, 2H); 4.1 (q, 2H); 5.2 (s, 2H); 6.9-7.0 (m, 3H); 7.1 (d, 1H); 7.4 (m, 1H); 7.5 (t, 1H); 7.8 (d, 1H).

Step C: Preparation of 4-(2-(2,6-Difluorobenzoyloxy)phenyl)-4-oxobutyric acid:

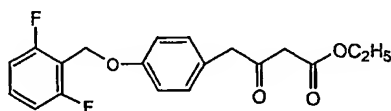
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Using the method of Example 21, Step C, the title compound was obtained.

$^1\text{H}$  NMR (270 MHz,  $\text{CDCl}_3$ ): 2.6 (t, 2H); 3.2 (t, 2H); 5.2 (s, 2H); 6.9-7.0 (m, 3H); 7.1 (d, 1H); 7.4 (m, 1H); 7.5 (t, 1H); 7.8 (d, 1H).

15

EXAMPLE 28: Synthesis of Ethyl 4-(4-(2,6-difluorobenzoyloxy)phenyl)methyl-3-oxobutylate



20

Step A: Preparation of Ethyl 4-hydroxybenzylate:

To a stirred solution of 4-Hydroxybenzyl alcohol (4 g, 26.28 mmol) in dry DMF (15 ml), pyridine (1 ml) and N,N-Dicyclohexylcarbodiimide (6.50 g, 31.5 mmol) was added abs EtOH (3.26 g, 78.84 mmol). The reaction mixture was stirred for 18 hours at room temperature and then filtered. The filtrate was concentrated under reduced pressure and purified by flash chromatography on silica gel column (hex: ethyl acetate, 2:1) to provide the title compound.

30  $^1\text{H}$  NMR (270 MHz,  $\text{CDCl}_3$ ): 1.2 (t, 3H); 3.5 (s, 2H); 4.1 (q, 2H); 6.7 (d, 2H); 7.1 (d, 2H).

Step B: Preparation of Ethyl 4-(2,6-difluorobenzyloxy)benzylate:

To a solution of NaH (60% dispersed in oil, .393 g, 9.8 mmol) in dry DMF (20 ml) was added Ethyl 4-hydroxybenzylate (Step A, 1.59 g, 8.8 mmol). When the evolution of hydrogen ceased, 2,6-Difluorobenzyl bromide (1.64 g, 7.9 mmol) was added. The reaction mixture was stirred for 4 hours at room temperature, quenched with sat.  $\text{NH}_4\text{Cl}$ , and concentrated in vacuo. The residue was taken in EtOAc and washed twice with water and brine. The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered, concentrated and purified by flash chromatography on silica gel column (hex: ethyl acetate, 2:1) to provide the title compound.

$^1\text{H}$  NMR (270 MHz,  $\text{CDCl}_3$ ): 1.2 (t, 3H); 3.5 (s, 2H); 4.1 (q, 2H); 5.1 (s, 2H); 6.9 (m, 4H); 7.2-7.4 (m, 3H).

Step C: Preparation of 4-(2,6-Difluorobenzyloxy)benzylic acid:

To a stirred solution of Ethyl 4-(2,6-difluorobenzyloxy)benzylate (Step B, 2.14 g, 6.9 mmol) in abs EtOH (30 ml) was added 1N NaOH (10 ml) at room temperature. The reaction mixture was stirred for 3 hours, acidified by 1M HCl and filtered. The white precipitate was washed with water and dried under high vacuum to provide the title compound.

$^1\text{H}$  NMR (270 MHz,  $\text{CDCl}_3$ ): 3.6 (s, 2H); 5.1 (s, 2H); 6.9 (m, 4H); 7.2-7.4 (m, 3H).

Step D: preparation of 4-(2,6-Difluorobenzyloxy)benzylcarbonyl chloride:

Thionyl chloride (10 ml) was added to 4-(2,6 Difluorobenzyloxy)benzylic acid (Step C, 1.61 g, 5.79 mmol). The reaction mixture was refluxed for 3 hours and concentrated in vacuo to provide light yellow oil which was used without further purification.

Ethyl 4-(4-(2,6-difluorobenzyloxy)phenyl)methyl-3-oxobutyrates:

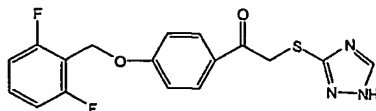
To a solution of Meldrum's acid (.846 g, 5.8 mmol) in dichloromethane (5 ml) was added pyridine (2 ml) over a period of 10 minutes at  $0^\circ\text{C}$ . To this solution was added 4-(2,6-Difluorobenzyloxy)benzylcarbonyl chloride (Step D, 1.71 g, 5.7 mmol) in

dichloromethane (5 ml), which resulted in an orange solution. The dark orange solution was stirred for 1 hour at 0°C, allowed to warm to room temperature and stirred for an additional hour. The reaction mixture was diluted with dichloromethane and poured onto 2M HCl and ice. The phases were separated and the aqueous phase was extracted  
5 twice with dichloromethane. The combined organic layers were washed twice with 2M HCl and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to a solid. The solid was suspended in abs EtOH (15 ml) and refluxed for 2.5 hours. The solvent was removed in vacuo to give a dark oil. The residue was purified by flash chromatography on silica gel column (hex: ethyl acetate, 2:1) to provide the title compound as a white solid.

10

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 1.2 (t, 3H); 3.4 (s, 2H); 3.7 (s, 2H); 4.2 (q, 2H); 5.1 (s, 2H); 6.9 (m, 4H); 7.1 (d, 2H); 7.3 (m, 1H).

EXAMPLE 29: Synthesis of 3-(2-(4-(2,6-Difluorobenzoyloxy)phenyl)-2-oxoethyl)thio-  
15 (1H-1,2,4)-triazole



20 Step A: Preparation of 4-(2,6-Difluorobenzoyloxy)acetophenone:

Using the method of Example 8, Step A, the title compound was obtained.

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 2.5 (s, 3H); 5.2 (s, 2H); 6.9-7.0 (m, 4H); 7.3-7.4 (m, 1H);  
25 7.9 (d, 2H).

Step B: Preparation of 2-Bromo-1-(4-(2,6-difluorobenzoyloxy)phenyl)-1-Ethanone:

To a stirred solution of copper (2) bromide (3.70 g, 16.6 mmol) in ethyl acetate (20 ml)  
30 was added a solution of 4-(2,6-Difluorobenzoyloxy)acetophenone ( Step A, 2.74 g, 10.4 mmol) in chloroform (20 ml) at room temperature. The reaction mixture was refluxed for 16 hours and then water was added. The crude mixture was extracted twice with

EtOAc. The organic layers were combined and washed with water, brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered, concentrated and purified by flash chromatography on silica gel column (hex: ethyl acetate, 4:1) to provide the title compound as a white flaky solid.

- 5  $^1\text{H}$  NMR (270 MHz,  $\text{CDCl}_3$ ): 4.4 (s, 2H); 5.2 (s, 2H); 6.9-7.1 (m, 4H), 7.3 (m, 1H); 8.0 (d, 2H).

Step C: Preparation of 3-(2-(4-(2,6-Difluorobenzyloxy)phenyl)-2-oxoethyl)thio-(1H-1,2,4)-triazole:

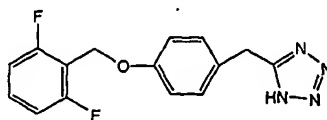
10

To a solution of 1H-1,2,4-Triazole-3-thiol (.250 g, 2.4 mmol) and triethylamine (2.50 g, 2.4 mmol) in dry dichloromethane (20 ml) was added 2-Bromo-1-(4-(2,6-difluorobenzyloxy)phenyl)-1-Ethanone (Step B, .851 g, 2.4 mmol) in dry dichloromethane (5 ml) at room temperature. The reaction mixture was stirred for 50 minutes and then concentrated in vacuo. The crude residue was taken in EtOAc and washed with .1M HCl, and brine. The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered, concentrated and purified by flash chromatography on silica gel column (chloroform: methanol, 9:1) to provide the title compound.

- 15  $^1\text{H}$  NMR (270 MHz,  $\text{CDCl}_3$ ): 4.5 (s, 2H); 5.1 (s, 2H); 6.8-7.0 (m, 4H), 7.2 (m, 1H); 7.9 (d, 2H); 8.0 (s, 1H).

EXAMPLE 30: Synthesis of 5-((4-(2,6-Difluorobenzyloxy)phenyl)-methyl)-1H-tetrazole

25



Step A: Preparation of (4-(2,6-Difluorobenzyloxy)phenyl)-acetonitrile:

- 30 To a solution of 4-Hydroxybenzyl cyanide (5 g, 37.5 mmol) and  $\text{K}_2\text{CO}_3$  (6.74 g, 48.8 mmol) in dry DMF (20 ml) was added 2,6-Difluorobenzyl bromide (7.77 g, 37.5 mmol). The reaction mixture was stirred for 4 hours at room temperature and

concentrated in vacuo. The crude residue was taken in EtOAc and washed with water and brine. The aqueous layer was washed one more time with EtOAc. The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to provide the title compound as a white solid.

5

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 3.65 (s, 2H); 5.1 (s, 2H); 6.9-7.0 (m, 4H); 7.2-7.4 (m, 3H);

Step B: Preparation of 5-((4-(2,6-Difluorobenzoyloxy)phenyl)-methyl)-1H-tetrazole:

10

A mixture of (4-(2,6-Difluorobenzoyloxy)phenyl)-acetonitrile (Step A, 5 g, 19.3 mmol), NaN<sub>3</sub> (1.3 g, 20 mmol), and NH<sub>4</sub>Cl (1.06 g, 20 mmol) in dry DMF (60 ml) was heated at 90°C for 16 hours. The solvent was removed in vacuo and the oily residue was partitioned between EtOAc and water (acidified to pH 1 with conc. HCl). The organic layer was washed with water, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to a brown semisolid. The purification was done by flash chromatography on silica gel column (chloroform: methanol, 9:1) to provide the title compound as a light creamy solid.

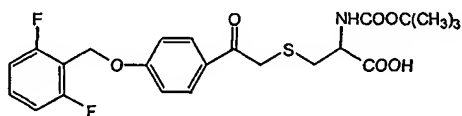
15

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 4.0 (s, 2H); 5.1 (s, 2H); 6.7-6.9 (m, 4H); 7.0 (d, 2H); 7.2 (m, 1H).

20

EXAMPLE 31: Synthesis of (2RS) 2-(N-Boc)-3-[2-(4-(2,6-difluorobenzoyloxy)phenyl)-2-oxoethyl] thiopropionic acid

25



Step A: Preparation of 4-(2,6-Difluorobenzoyloxy)acetophenone:

30

To a solution of 4-Hydroxyacetophenone (3.28 g, 24 mmol) and K<sub>2</sub>CO<sub>3</sub> (4.33 g, 31.3 mmol) in dry DMF (15 ml) was added 2,6-Difluorobenzyl bromide (5 g, 24.1 mmol).



The reaction mixture was stirred at room temperature for 5 hours, quenched with water and concentrated in vacuo. The crude residue was taken in EtOAc and washed with water and brine. The aqueous layer was extracted twice with EtOAc. The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated and purified by flash chromatography on silica gel column (hex: ethyl acetate, 2:1) to provide the title compound.

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 2.5 (s, 3H); 5.2 (s, 2H); 6.9-7.0 (m, 4H); 7.3-7.4 (m, 1H); 7.9 (d, 2H).

Step B: Preparation of 2-Bromo-1-(4-(2,6-difluorobenzyloxy) phenyl)-1-Ethanone:

Using the method of Example 29, Step B, the title compound was obtained.

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 4.4 (s, 2H); 5.2 (s, 2H); 6.9-7.1 (m, 4H), 7.3 (m, 1H); 8.0 (d, 2H).

Step C: Preparation of Ethyl (2RS) 2-(N-Boc)-3-[2-(4-(2,6-difluorobenzyloxy)phenyl)-2-oxoethyl] thiopropionate:

To a stirred solution of 2-Bromo-1-(4-(2,6-difluorobenzyloxy)phenyl)-1-Ethanone (Step B, 2.07 g, 8.3 mmol) in dry dichloromethane (20 ml) and triethylamine (8.39 g, 83 mmol) was added Boc-Cys-OEt (2.94 g, 8.6 mmol). The reaction mixture was stirred at room temperature for an hour and concentrated in vacuo. The crude residue was taken in EtOAc, washed with .1M HCl, and brine. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated and purified by flash chromatography on silica gel column (chloroform: methanol, 97.5:2.5) to provide the title compound.

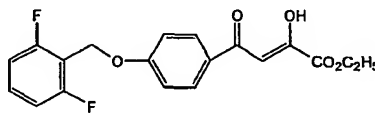
<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 1.2 (t, 3H); 1.4 (s, 9H); 3.0 (m, 2H); 3.8 (s, 2H); 4.2 (q, 2H); 4.5 (br, 1H); 5.2 (s, 2H); 5.4 (d, 1H); 6.9-7.1 (m, 4H); 7.3 (m, 1H); 7.9 (d, 2H).

Step D: Preparation of (2RS) 2-(N-Boc)-3-[2-(4-(2,6-difluorobenzyloxy)phenyl)-2-oxoethyl] thiopropionic acid:

To a solution of Ethyl (2RS) 2-(N-Boc)-3-[2-(4-(2,6-difluorobenzyloxy)phenyl)-2-oxoethyl] thiopropionate (Step C, .761 g, 1.5 mmol) in abs EtOH (10 ml) was added 1N NaOH (3 ml). The reaction mixture was stirred at room temperature for 4 hours, acidified with 1M HCl and concentrated in vacuo. The crude residue was taken in  
5 chloroform, and washed with water and brine. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated and purified by flash chromatography on silica gel column (chloroform: methanol, 92.7:7.5) to provide the title compound.

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 1.4 (s, 9H); 3.0 (t, 2H); 4.0 (q, 2H); 4.5 (br, 1H); 5.2 (s,  
10 2H); 5.4 (d, 1H); 6.9-7.1 (m, 4H); 7.3 (m, 1H); 7.9 (d, 2H).

EXAMPLE 32: Synthesis of Ethyl 2-Hydroxy-4-oxo-4-(4-(2,6-difluorobenzyloxy)phenyl) but-2-enoate



15

Step A: Preparation of 4-(2,6-Difluorobenzyloxy)acetophenone:

Using the method of example 31, Step A, the title compound was obtained.

20

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 2.5 (s, 3H); 5.2 (s, 2H); 6.9-7.0 (m, 4H); 7.3-7.4 (m, 1H); 7.9 (d, 2H).

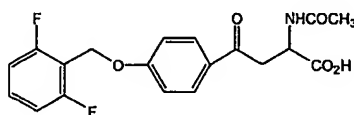
Step B: Preparation of Ethyl 2-Hydroxy-4-oxo-4-(4-(2,6-difluorobenzyloxy)phenyl)  
25 but-2-enoate:

A mixture of 4-(2,6-Difluorobenzyloxy)acetophenone (Step A, 5.64 g, 21.5 mmol) and diethyl oxalate (3.14 g, 21.5 mmol) was added to an ice-cooled solution of NaOEt (.490 g, 22.4 mmol of metallic Na) in abs EtOH (25 ml). After being allowed to stand  
30 overnight at room temperature, the mixture was diluted with water (50 ml), acidified with 10% HCl, and extracted thrice with EtOAc. The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated and purified by flash

chromatography on silica gel column (hex: ethyl acetate, 4:1) to provide the title compound.

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 1.4 (t, 3H); 4.4 (q, 2H); 5.2 (s, 2H); 6.9-7.1 (m, 5H); 7.3-7.4 (m, 1H); 8.0 (d, 2H).

EXAMPLE 33: Synthesis of (2RS) 2-(N-Acetyl)-4-(4-(2,6-difluorobenzoyloxy) phenyl)-4-oxobutyrac acid



Step A: Preparation of 4-(2,6-Difluorobenzoyloxy)acetophenone:

Using the method of example 31, Step A, the title compound was obtained.

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 2.5 (s, 3H); 5.2 (s, 2H); 6.9-7.0 (m, 4H); 7.3-7.4 (m, 1H); 7.9 (d, 2H).

Step B: Preparation of 2-Bromo-1-(4-(2,6-difluorobenzoyloxy) phenyl)-1-Ethanone:  
Using the method of Example 29, Step B, the title compound was obtained.

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 4.4 (s, 2H); 5.2 (s, 2H); 6.9-7.1 (m, 4H); 7.3 (m, 1H); 8.0 (d, 2H).

Step C: Preparation of Diethyl (N-Acetyl)(2-(4-(2,6-difluorobenzoyloxy)phenyl)-2-oxoethyl)propanedioate:

To a solution of Diethyl acetamidomalonate (.949 g, 4.3 mmol) and NaOEt (.301 g, 4.4 mmol) in abs EtOH (25 ml) was added 2-Bromo-1-(4-(2,6-difluorobenzoyloxy) phenyl)-1-Ethanone (Step B, 1.42 g, 4.1 mmol). The reaction mixture was stirred at room temperature for 2 hours and concentrated in vacuo. The crude residue was partitioned

between EtOAc and .01 N NaOH. The organic layer was washed with water and .001 M HCl, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The purification was done by flash chromatography on silica gel column (hex: ethyl acetate, 2:1) to provide the title compound.

5

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 1.2 (t, 6H); 2.0 (s, 3H); 4.2-4.3 (m, 6H); 5.2 (s, 2H); 6.9-7.1 (m, 4H), 7.3-7.4 (m, 1H); 7.9 (d, 2H).

Step D: Preparation of (2RS) 2-(N-Acetyl)-4-(4-(2,6-difluorobenzyloxy)phenyl)-4-oxobutyric acid:

10

To a solution of Diethyl (N-Acetyl)(2-(4-(2,6-difluorobenzyloxy)phenyl)-2-oxoethyl)propanedioate (Step C, 1.28 g, 2.6 mmol) in water (20 ml) was added NaOH (.529 g, 13.2 mmol). The reaction mixture was refluxed for 16 hours, then glacial acetic acid (18 ml) was added and refluxing continued for an additional 3 hours. The mixture was concentrated in vacuo and purified by flash chromatography on silica gel column (chloroform: methanol, 9:1) to provide the title compound.

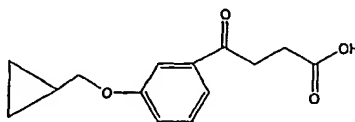
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<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>:CD<sub>3</sub>OD): 2.0 (s, 3H); 3.5 (m, 2H); 4.8 (t, 1H); 5.1 (s, 2H); 6.9-7.1 (m, 4H), 7.3-7.4 (m, 1H); 7.9 (d, 2H).

20

EXAMPLE 34: Synthesis of 4-(3-((Cyclopropyl)-methoxy)phenyl)-4-oxobutyric acid

25



Step A: Preparation of 3-((Cyclopropyl)-methoxy)acetophenone:

Using the method of Example 31, Step A, using Cyclopropylmethyl bromide and 3-Hydroxyacetophenone as the starting materials, the title compound was obtained.

30

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): .4 (m, 2H); .6 (m, 2H); 1.2 (m, 1H); 2.5 (s, 3H); 3.8 (d, 2H); 7.1 (m, 1H); 7.4 (m, 1H); 7.5-7.6 (m, 2H).

Step B: Preparation of tert-Butyl 4-(3-((cyclopropyl)-methoxy)phenyl)-4-oxobutyrat:

5

Using the method of Example 8, Step B, the title compound was obtained.

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): .4 (m, 2H); .6 (m, 2H); 1.2 (m, 1H); 1.4 (s, 9H); 2.6 (t, 2H); 3.2 (t, 2H); 3.8 (d, 2H); 7.1 (m, 1H); 7.4 (m, 1H); 7.5-7.6 (m, 2H).

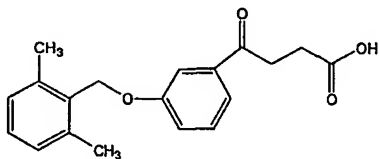
10

Step C: Preparation of 4-(3-((Cyclopropyl)-methoxy)phenyl)-4-oxobutyric acid:

Using the method of Example 8, Step C, the title compound was obtained.

15 <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): .4 (m, 2H); .6 (m, 2H); 1.2 (m, 1H); 2.8 (t, 2H); 3.2 (t, 2H); 3.8 (d, 2H); 7.1 (m, 1H); 7.4 (m, 1H); 7.5-7.6 (m, 2H).

EXAMPLE 35: Synthesis of 4-(3-(2,6-Dimethylbenzyloxy)phenyl)-4-oxobutyric acid



20

Step A: Preparation of 2,6-Dimethylbenzyl Alcohol:

To a solution of 2,6-dimethylbenzoic acid (10 g, 66.5 mmol) and potassium carbonate (9.18 g, 66.5 mmol) in dimethylformamide (67 ml), was added methyl iodide (8.28 ml, 133.16 ml) in an ice bath, and the mixture was stirred for 16 hours. To the reaction mixture was added toluene and water, and the organic layer was washed with 3% K<sub>2</sub>CO<sub>3</sub>,

1N HCl, and brine. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated.

30 The oily residue was redissolved in dry THF (135 ml), added to LiAlH<sub>4</sub> (3.79 g, 99.8 mmol), and stirred for 4 hours in an ice bath. To the reaction mixture was added 1N

HCl slowly followed by ethyl acetate, and the organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The oily residue was used without further purification.

5    <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 2.4 (s, 6H); 4.7 (s, 2H); 7.0-7.15 (m, 3H).

Step B: Preparation of 3-(2,6-Dimethylbenzyloxy)acetophenone:

To a stirred solution of 3'-Hydroxyacetophenone (8.07 g, 59.24 mmol) and  
10    Triphenylphosphine (16.93 g, 64.5 mmol) in dry THF (180 ml) was added dropwise  
2,6-Dimethylbenzyl alcohol (8.05 g, 59.24 mmol) and diethyl azodicarboxylate (11.24  
g, 64.57 mmol) in dry THF (45 ml) and dry DMF (18 ml) at ambient temperature. After  
stirring for 1.5 hours at ambient temperature, the reaction mixture was diluted with  
ether and washed twice with water, 1N NaOH and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered  
15    and concentrated. The purification was done by flash chromatography on silica gel  
column (hex: ethyl acetate, 2:1) to provide the title compound.

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 2.4 (s, 6H); 2.6 (s, 3H); 5.1 (s, 2H); 7.1 (dd, 2H); 7.2 (m,  
2H); 7.4 (t, 1H); 7.6 (m, 2H).  
20

Step C: Preparation of Ethyl 4-(3-(2,6-dimethylbenzyloxy)phenyl)-4-oxobutyrates:

Using the method of Example 17, Step B, the title compound was obtained.

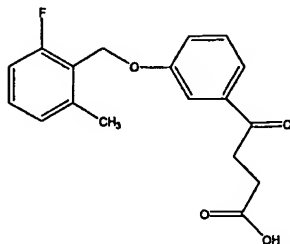
25    <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 1.2 (s, 3H); 2.4 (s, 6H); 2.8 (t, 2H); 3.2 (t, 2H); 4.4 (q,  
2H); 5.1 (s, 2H); 7.1 (d, 2H); 7.2 (m, 2H); 7.4 (t, 1H); 7.6 (m, 2H).

Step D: Preparation of 4-(3-(2,6-Dimethylbenzyloxy)phenyl)-4-oxobutyric acid:

30    To a solution of Ethyl 4-(3-(2,6-dimethylbenzyloxy)phenyl)-4-oxobutyrates (Step C,  
12.31 g, 36.2 mmol) in abs ethanol (160 ml) was added 1N NaOH (50 ml) at room  
temperature. The reaction mixture was stirred for 3 hours and then acidified with 1M  
HCl. The occurring white precipitate was filtered, washed with water and dried under  
vacuum to provide the title compound as a white solid.

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 2.4 (s, 6H); 2.8(t, 2H); 3.3 (t, 2H); 5.1 (s, 2H); 7.1 (d, 2H); 7.2-7.3 (m, 2H); 7.4 (t, 1H); 7.6 (m, 2H).

EXAMPLE 36: Synthesis of 4-(3-(2-Fluoro-6-methylbenzyloxy)phenyl)-4-oxobutyr-  
5 acid:



Step A: Preparation of 2-Fluoro-6-methylbenzoic Acid:

10 Synthesized as described in Example 89(d) of International Patent Publication No. WO 97/34893, page 43.

Step B: Preparation of 2-Fluoro-6-methylbenzyl Alcohol:

15 Using the method of Example 35, Step A, the title compound was obtained.

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 2.4 (s, 3H); 4.7 (s, 2H); 6.85 (t, 1H); 6.95 (d, 1H); 7.15 (m, 1H).

20 Step C: Preparation of 3-(2-Fluoro-6-methylbenzyloxy)acetophenone:

Using the method of Example 35, Step B, the title compound was obtained.

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 2.4 (s, 3H); 2.6 (s, 3H); 5.1 (s, 2H); 7.1 (m, 2H); 7.2 (m, 2H); 7.4 (t, 1H); 7.6 (m, 2H).

Step D: Preparation of Ethyl 4-(3-(2-Fluoro-6-methylbenzyloxy)phenyl)-4-oxobutyr-  
25 ate:

Using the method of Example 17, Step B, the title compound was obtained.

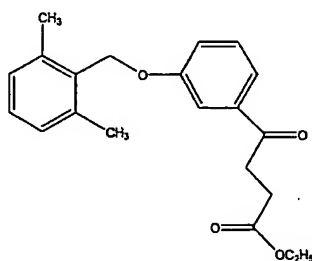
$^1\text{H}$  NMR (270 MHz,  $\text{CDCl}_3$ ): 1.2 (s, 3H); 2.4 (s, 3H); 2.8 (t, 2H); 3.3 (t, 2H); 4.4 (q, 2H); 5.2 (s, 2H); 6.9-7.1 (m, 2H); 7.2 (m, 2H); 7.4 (t, 1H); 7.6 (m, 2H).

5 Step E: Preparation of 4-(3-(2-Fluoro-6-methylbenzyloxy)phenyl)-4-oxobutyrac acid:

To a solution of Ethyl 4-(3-(2-Fluoro-6-methylbenzyloxy)phenyl)-4-oxobutyrac (Step D, 8.56 g, 24.9 mmol) in abs ethanol (100 ml) was added 1N NaOH (40 ml) at room temperature. The reaction mixture was stirred for 3 hours, acidified with 1M HCl and  
10 concentrated. The residue was taken in chloroform and washed with .1 M HCl, brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated. The purification was done by flash chromatography on silica gel column (chloroform: methanol 95:5 spiked with acetic acid) to provide the title compound as white solid.

15  $^1\text{H}$  NMR (270 MHz,  $\text{CDCl}_3$ ): 2.4 (s, 3H); 2.8 (t, 2H); 3.3 (t, 2H); 5.1 (s, 2H); 6.9-7.1 (m, 2H); 7.2 (m, 2H); 7.4 (t, 1H); 7.6 (m, 2H).

EXAMPLE 37: Synthesis of Ethyl 4-(3-(2,6-dimethylbenzyloxy)phenyl)-4-oxobutyrac:  
20



25 Step A: Preparation of 2,6-Dimethylbenzyl Alcohol:

Using the method of Example 35, Step A, the title compound was obtained.

$^1\text{H}$  NMR (270 MHz,  $\text{CDCl}_3$ ): 2.4 (s, 6H); 4.7 (s, 2H); 7.0-7.15 (m, 3H).



Step B: Preparation of 3-(2,6-Dimethylbenzyloxy)acetophenone:

Using the method of Example 35, Step B, the title compound was obtained.

5

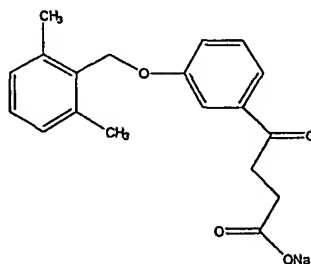
$^1\text{H}$  NMR (270 MHz,  $\text{CDCl}_3$ ): 2.4 (s, 6H); 2.6 (s, 3H); 5.1 (s, 2H); 7.1 (dd, 2H); 7.2 (m, 2H); 7.4 (t, 1H); 7.6 (m, 2H).

Step C: Preparation of Ethyl 4-(3-(2,6-dimethylbenzyloxy)phenyl)-4-oxobutyrates:

10 Using the method of Example 17, Step B, the title compound was obtained.

$^1\text{H}$  NMR (270 MHz,  $\text{CDCl}_3$ ): 1.2 (s, 3H); 2.4 (s, 6H); 2.8 (t, 2H); 3.2 (t, 2H); 4.4 (q, 2H); 5.1 (s, 2H); 7.1 (d, 2H); 7.2 (m, 2H); 7.4 (t, 1H); 7.6 (m, 2H).

15 **EXAMPLE 38:** Synthesis of 4-(3-(2,6-Dimethylbenzyloxy)phenyl)-4-oxobutyric acid Sodium salt:



20 Step A: Preparation of 2,6-Dimethylbenzyl Alcohol:

Using the method of Example 35, Step A, the title compound was obtained.

$^1\text{H}$  NMR (270 MHz,  $\text{CDCl}_3$ ): 2.4 (s, 6H); 4.7 (s, 2H); 7.0-7.15 (m, 3H).

25

Step B: Preparation of 3-(2,6-Dimethylbenzyloxy)acetophenone:

Using the method of Example 35, Step B, the title compound was obtained.

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 2.4 (s, 6H); 2.6 (s, 3H); 5.1 (s, 2H); 7.1 (dd, 2H); 7.2 (m, 2H); 7.4 (t, 1H); 7.6 (m, 2H).

Step C: Preparation of Ethyl 4-(3-(2,6-dimethylbenzyloxy)phenyl)-4-oxobutyrates:

5 Using the method of Example 17, Step B, the title compound was obtained.

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 1.2 (s, 3H); 2.4 (s, 6H); 2.8 (t, 2H); 3.2 (t, 2H); 4.4 (q, 2H); 5.1 (s, 2H); 7.1 (d, 2H); 7.2 (m, 2H); 7.4 (t, 1H); 7.6 (m, 2H).

10 Step D: Preparation of 4-(3-(2,6-Dimethylbenzyloxy)phenyl)-4-oxobutyric acid:

Using the method of Example 36, Step E, the title compound was obtained.

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 2.4 (s, 6H); 2.8 (t, 2H); 3.3 (t, 2H); 5.1 (s, 2H); 7.1 (d, 2H); 7.2-7.3 (m, 2H); 7.4 (t, 1H); 7.6 (m, 2H).

Step E: Preparation of 4-(3-(2,6-Dimethylbenzyloxy)phenyl)-4-oxobutyric acid

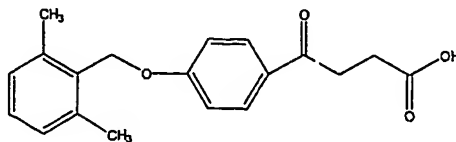
Sodium salt:

20 The 4-(3-(2,6-Dimethylbenzyloxy)phenyl)-4-oxobutyric acid (Step D, 5.5 g, 17.6 mmol) was dissolved in abs ethanol (20 ml) by warming gently followed by addition of NaOH (0.705 g) at 0°C temperature. The reaction mixture was stirred for one hour, concentrated in vacuo and lyophilized to give as a white solid.

25 <sup>1</sup>H NMR (270 MHz, D<sub>2</sub>O): 2.0 (s, 6H); 2.5 (t, 2H); 3.0 (t, 2H); 4.8 (s, 2H); 6.8 (d, 2H); 6.9 (m, 2H); 7.2 (t, 1H); 7.5 (d, 2H).

EXAMPLE 39: Synthesis of 4-(4-(2,6-Dimethylbenzyloxy)phenyl)-4-oxobutyric acid:

30



Step A: Preparation of 2,6-Dimethylbenzyl Alcohol:

Using the method of Example 35, Step A, the title compound was obtained.

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 2.4 (s, 6H); 4.7 (s, 2H); 7.0-7.15 (m, 3H).

5

Step B: Preparation of 4-(2,6-Dimethylbenzyloxy)acetophenone:

Using the method of Example 35, Step B, the title compound was obtained.

10 <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 2.4 (s, 6H); 2.6 (s, 3H); 5.1 (s, 2H); 7.0-7.2 (m, 5H); 8.0 (d, 2H).

Step C: Preparation of Ethyl 4-(4-(2,6-dimethylbenzyloxy)phenyl)-4-oxobutyrates:

15 Using the method of Example 17, Step B, the title compound was obtained.

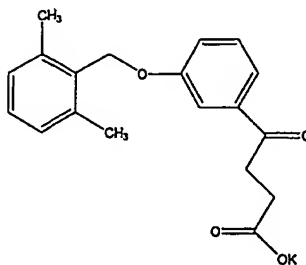
<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 1.2 (s, 3H); 2.4 (s, 6H); 2.8 (t, 2H); 3.3 (t, 2H); 4.4 (q, 2H); 5.1 (s, 2H); 7.0-7.2 (m, 5H); 8.0 (d, 2H).

20 Step D: Preparation of 4-(4-(2,6-Dimethylbenzyloxy)phenyl)-4-oxobutyric acid:

Using the method of Example 36, Step E, the title compound was obtained.

25 <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 2.4 (s, 6H); 2.8 (t, 2H); 3.3 (t, 2H); 5.1 (s, 2H); 7.0-7.2 (m, 5H); 8.0 (d, 2H).

EXAMPLE 40: Synthesis of 4-(3-(2,6-Dimethylbenzyloxy)phenyl)-4-oxobutyric acid  
Potassium salt:



5

Step A: Preparation of 2,6-Dimethylbenzyl Alcohol:

10 Using the method of Example 35, Step A, the title compound was obtained.

$^1\text{H}$  NMR (270 MHz,  $\text{CDCl}_3$ ): 2.4 (s, 6H); 4.7 (s, 2H); 7.0-7.15 (m, 3H).

Step B: Preparation of 3-(2,6-Dimethylbenzyloxy)acetophenone:

15

Using the method of Example 35, Step B, the title compound was obtained.

$^1\text{H}$  NMR (270 MHz,  $\text{CDCl}_3$ ): 2.3 (s, 6H); 2.6 (s, 3H); 5.1 (s, 2H); 7.1 (d, 2H); 7.2 (m, 2H); 7.45 (t, 1H); 7.6 (m, 2H).

20 Step C: Preparation of Ethyl 4-(3-(2,6-dimethylbenzyloxy)phenyl)-4-oxobutylate:

Using the method of Example 17, Step B, the title compound was obtained.

25  $^1\text{H}$  NMR (270 MHz,  $\text{CDCl}_3$ ): 1.2 (s, 3H); 2.4 (s, 6H); 2.8 (t, 2H); 3.2 (t, 2H); 4.4 (q, 2H); 5.1 (s, 2H); 7.1 (d, 2H); 7.2 (m, 2H); 7.45 (t, 1H); 7.6 (m, 2H).

Step D: Preparation of 4-(3-(2,6-Dimethylbenzyloxy)phenyl)-4-oxobutyric acid:

Using the method of Example 36, Step E, the title compound was obtained.

$^1\text{H}$  NMR (270 MHz,  $\text{CDCl}_3$ ): 2.4 (s, 6H); 2.5 (t, 2H); 3.2 (t, 2H); 5.1 (s, 2H); 7.1 (d, 2H); 7.2-7.3 (m, 2H); 7.45 (t, 1H); 7.6 (m, 2H).

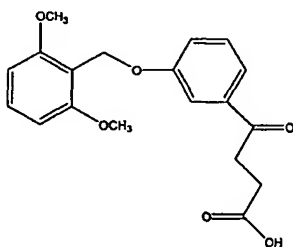
Step E: Preparation of 4-(3-(2,6-Dimethylbenzyloxy)phenyl)-4-oxobutyric acid

5 Potassium salt:

The 4-(3-(2,6-Dimethylbenzyloxy)phenyl)-4-oxobutyric acid (Step D, 6.0 g, 19.4 mmol) was dissolved in abs ethanol (20 ml) by warming gently followed by addition of KOH (1.21 g) at  $0^\circ\text{C}$  temperature. The reaction mixture was stirred for one hour,  
10 concentrated in vacuo and lyophilized to give the title compound as white solid.

$^1\text{H}$  NMR (270 MHz,  $\text{D}_2\text{O}$ ): 2.3 (s, 6H); 2.5 (t, 2H); 3.3 (t, 2H); 5.1 (s, 2H); 7.1 (d, 2H); 7.2-7.3 (m, 2H); 7.45 (t, 1H); 7.6 (m, 2H).

15 EXAMPLE 41: Synthesis of 4-(3-(2,6-Dimethoxybenzyloxy)phenyl)-4-oxobutyric acid:



20

Step A: Preparation of 2,6-Dimethoxybenzyl Alcohol:

25 Using the method of Example 35, Step A, the title compound was obtained.

$^1\text{H}$  NMR (270 MHz,  $\text{CDCl}_3$ ): 3.9 (s, 6H); 4.8 (s, 2H); 6.5 (d, 2H); 7.25 (m, 1H).

Step B: Preparation of 3-(2,6-Dimethoxybenzyloxy)acetophenone:

Using the method of Example 35, Step B, the title compound was obtained.

$^1\text{H}$  NMR (270 MHz,  $\text{CDCl}_3$ ): 2.6 (s, 3H); 3.9 (s, 6H); 5.2 (s, 2H); 6.6 (d, 2H); 7.3 (m, 3H); 7.5 (d, 1H); 7.7 (d, 1H).

5

Step C: Preparation of Ethyl 4-(3-(2,6-dimethoxybenzyloxy)phenyl)-4-oxobutyrates:

Using the method of Example 17, Step B, the title compound was obtained.

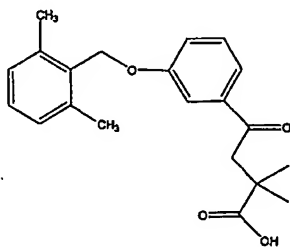
10  $^1\text{H}$  NMR (270 MHz,  $\text{CDCl}_3$ ): 1.2 (t, 3H); 2.8 (t, 2H); 3.3 (t, 2H); 3.8 (s, 6H); 4.1 (q, 2H); 5.2 (s, 2H); 6.5 (d, 2H); 7.3-7.4 (m, 3H); 7.6 (d, 1H); 7.7 (d, 1H).

Step D: Preparation of 4-(3-(2,6-dimethoxybenzyloxy)phenyl)-4-oxobutyric acid:

15 Using the method of Example 36, Step E, the title compound was obtained.

$^1\text{H}$  NMR (270 MHz,  $\text{CDCl}_3$ ): 2.8 (t, 2H); 3.3 (t, 2H); 3.8 (s, 6H); 5.2 (s, 2H); 6.5 (d, 2H); 7.3-7.4 (m, 3H); 7.6 (d, 1H); 7.7 (d, 1H).

20 **EXAMPLE 42:** Synthesis of 4-(3-(2,6-Dimethylbenzyloxy)phenyl)-4-oxo-2,2-dimethylbutyric acid:



Step A: Preparation of 2,6-Dimethylbenzyl Alcohol:

25 Using the method of Example 35, Step A, the title compound was obtained.

$^1\text{H}$  NMR (270 MHz,  $\text{CDCl}_3$ ): 2.4 (s, 6H); 4.7 (s, 2H); 7.0-7.15 (m, 3H).

Step B: Preparation of 3-(2,6-Dimethylbenzyloxy)acetophenone:

Using the method of Example 35, Step B, the title compound was obtained.

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 2.4 (s, 6H); 2.6 (s, 3H); 5.1 (s, 2H); 7.1 (dd, 2H); 7.2 (m, 2H); 7.4 (t, 1H); 7.6 (m, 2H).

Step C: Preparation of Ethyl 4-(3-(2,6-dimethylbenzyloxy)phenyl)-4-oxo-2,2-dimethylbutyrate:

To a stirred solution of 3-(2,6-Dimethylbenzyloxy)acetophenone (Step B, 4.11 g, 16.1 mmol) in dry THF (60 ml) and DMPU (12 ml) was added a solution of lithium bis(trimethylsilyl)amide (1.0M, 17.74 ml) at -60°C under argon. After stirring for 10 minutes at -60°C, Ethyl 2-bromoisobutyrate (4.73 g, 24.2 mmol) was added rapidly. The reaction mixture was stirred for an additional 10 minutes and then warmed to room temperature for 4 hours. The crude mixture was taken in EtOAc and washed with water. The aqueous layer was extracted one more time with EtOAc. The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated and purified by flash chromatography on silica gel column (hex: ethyl acetate, 4:1) to provide the title compound as white solid.

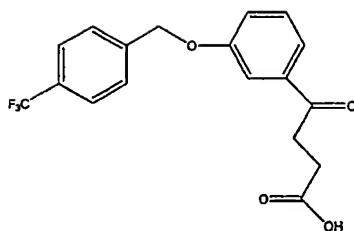
<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 1.2 (t, 3H); 1.3 (s, 6H); 2.3 (s, 6H); 3.3 (s, 2H); 4.1 (q, 2H); 5.1 (s, 2H); 7.1 (d, 2H); 7.2 (m, 2H); 7.4 (t, 1H); 7.6 (m, 2H).

Step D: Preparation of 4-(3-(2,6-Dimethylbenzyloxy)phenyl)-4-oxo-2,2-dimethylbutyric acid:

Using the method of Example 36, Step E, the title compound was obtained.

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 1.3 (s, 6H); 2.3 (s, 6H); 3.3 (s, 2H); 5.1 (s, 2H); 7.1 (d, 2H); 7.2 (m, 2H); 7.4 (t, 1H); 7.6 (m, 2H).

EXAMPLE 43: Synthesis of 4-(3-(4-(Trifluoromethyl)benzyloxy)phenyl)-4-oxobutyric acid:



Step A: Preparation of 3-(4-(Trifluoromethyl)benzyloxy)acetophenone:

5

Using the method of Example 31, Step A, using 4-(Trifluoromethyl)benzyl bromide and 3-Hydroxyacetophenone as the starting materials, the title compound was obtained.

$^1\text{H}$  NMR (270 MHz,  $\text{CDCl}_3$ ): 2.5 (s, 3H); 5.1 (s, 2H); 7.1 (d, 2H); 7.4-7.6 (m, 6H).

10

Step B: Preparation of Ethyl 4-(3-(4-(trifluoromethyl)benzyloxy)phenyl)-4-oxobutylate:

Using the method of Example 17, Step B, the title compound was obtained.

15

$^1\text{H}$  NMR (270 MHz,  $\text{CDCl}_3$ ): 1.3 (t, 3H); 2.7 (t, 2H); 3.3 (t, 2H); 4.1 (q, 2H); 5.1 (s, 2H); 7.1 (d, 2H); 7.4-7.6 (m, 6H).

Step C: Preparation of 4-(3-(4-(Trifluoromethyl)benzyloxy)phenyl)-4-oxobutyric acid:

20

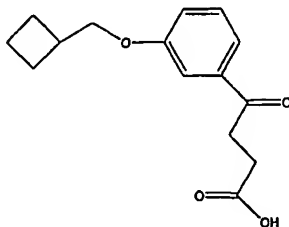
Using the method of Example 36, Step E, the title compound was obtained.

$^1\text{H}$  NMR (270 MHz,  $\text{CDCl}_3$ ): 2.7 (t, 2H); 3.3 (t, 2H); 5.1 (s, 2H); 7.1 (d, 2H); 7.4-7.6 (m, 6H).

25



EXAMPLE 44: Synthesis of 4-(3-((Cyclobutyl)-methoxy)phenyl)-4-oxobutyric acid:



5 Step A: Preparation of 3-((Cyclobutyl)-methoxy)acetophenone:

Using the method of Example 31, Step A, using Cyclobutylmethyl bromide and 3-Hydroxyacetophenone as the starting materials, the title compound was obtained.

10  $^1\text{H}$  NMR (270 MHz,  $\text{CDCl}_3$ ): 1.9 (m, 4H); 2.1 (m, 2H); 2.5 (s, 3H); 2.7 (m, 1H); 4.0 (d, 2H); 7.1 (dd, 1H); 7.4 (t, 1H); 7.5-7.6 (m, 2H).

Step B: Preparation of Ethyl 4-(3-((cyclobutyl)-methoxy)phenyl)-4-oxobutyrate:

15 Using the method of Example 35, Step C, the title compound was obtained.

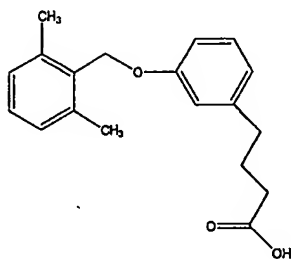
$^1\text{H}$  NMR (270 MHz,  $\text{CDCl}_3$ ): 1.2 (t, 3H); 1.9 (m, 4H); 2.1 (m, 2H); 2.7 (m, 1H); 2.8 (t, 2H); 3.3 (t, 2H); 4.0 (d, 2H); 4.1 (q, 2H); 7.1 (dd, 1H); 7.4 (t, 1H); 7.5-7.6 (m, 2H).

20 Step C: Preparation of 4-(3-((Cyclobutyl)-methoxy)phenyl)-4-oxobutyric acid:

Using the method of Example 36, Step E, the title compound was obtained.

25  $^1\text{H}$  NMR (270 MHz,  $\text{CDCl}_3$ ): 1.9 (m, 4H); 2.1 (m, 2H); 2.7 (m, 1H); 2.8 (t, 2H); 3.3 (t, 2H); 4.0 (d, 2H); 7.1 (dd, 1H); 7.4 (t, 1H); 7.5-7.6 (m, 2H).

EXAMPLE 45: Synthesis of 4-(3-(2,6-Dimethylbenzyloxy)phenyl)butyric acid:



5 Step A: Preparation of 2,6-Dimethylbenzyl Alcohol:

Using the method of Example 35, Step A, the title compound was obtained.

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 2.4 (s, 6H); 4.7 (s, 2H); 7.0-7.15 (m, 3H).

10

Step B: Preparation of 3-(2,6-Dimethylbenzyloxy)acetophenone:

Using the method of Example 35, Step B, the title compound was obtained.

15 <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 2.4 (s, 6H); 2.6 (s, 3H); 5.1 (s, 2H); 7.1 (dd, 2H); 7.2 (m, 2H); 7.4 (t, 1H); 7.6 (m, 2H).

Step C: Preparation of Ethyl 4-(3-(2,6-dimethylbenzyloxy)phenyl)-4-oxobutrate:

20 Using the method of Example 17, Step B, the title compound was obtained.

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 1.2 (s, 3H); 2.4 (s, 6H); 2.8 (t, 2H); 3.2 (t, 2H); 4.4 (q, 2H); 5.1 (s, 2H); 7.1 (d, 2H); 7.2 (m, 2H); 7.4 (t, 1H); 7.6 (m, 2H).

Step D: Preparation of 4-(3-(2,6-Dimethylbenzyloxy)phenyl)-4-oxobutyric acid:

25

Using the method of Example 36, Step E, the title compound was obtained.

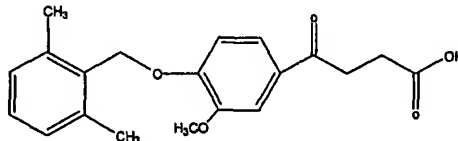
<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 2.4 (s, 6H); 2.8 (t, 2H); 3.3 (t, 2H); 5.1 (s, 2H); 7.1 (d, 2H); 7.2-7.3 (m, 2H); 7.4 (t, 1H); 7.6 (m, 2H).

Step E: Preparation of 4-(3-(2,6-Dimethylbenzyloxy)phenyl)butyric acid:

A solution of 4-(3-(2,6-Dimethylbenzyloxy)phenyl)-4-oxobutyric acid (Step D, 3 g, 9.6 mmol), hydrazine (1.41 ml, 28.8 mmol) and potassium hydroxide (1.61 g, 28.8 mmol) in ethylene glycol (12 ml) was refluxed for 4 h, water (18 ml) and 6 N HCl (10 ml) were added to the reaction mixture. The crude reaction mixture was concentrated, and the residue was dissolved in EtOAc, washed with water and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The purification was done by flash chromatography on silica gel column (chloroform:methanol 95:5 spiked with acetic acid) to provide the title compound as a white solid.

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 2.4 (m, 8H); 2.8 (t, 2H); 3.3 (t, 2H); 5.1 (s, 2H); 7.1 (d, 2H); 7.2-7.3 (m, 2H); 7.4 (t, 1H); 7.6 (m, 2H).

EXAMPLE 46: Synthesis of 4-[[4-(2,6-Dimethylbenzyloxy)-3-methoxy]phenyl]-4-oxobutyric acid:



Step A: Preparation of 2,6-Dimethylbenzyl Alcohol:

Using the method of Example 35, Step A, the title compound was obtained.

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 2.4 (s, 6H); 4.7 (s, 2H); 7.0-7.15 (m, 3H).

25

Step B: Preparation of 4-(2,6-Dimethylbenzyloxy)-3-methoxyacetophenone:

Using the method of Example 35, Step B, the title compound was obtained.

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 2.4 (s, 6H); 2.6 (s, 3H); 3.9 (s, 3H); 5.1 (s, 2H); 7.1 (d, 2H); 7.2 (m, 2H); 7.6 (m, 2H).

Step C: Preparation of Ethyl 4-[[4-(2,6-dimethylbenzyloxy)-3-methoxy]phenyl]-4-oxobutyrates:

Using the method of Example 17, Step B, the title compound was obtained.

5

$^1\text{H}$  NMR (270 MHz,  $\text{CDCl}_3$ ): 1.2 (s, 3H); 2.4 (s, 6H); 2.8 (t, 2H); 3.3 (t, 2H); 3.9 (s, 3H); 4.4 (q, 2H); 5.1 (s, 2H); 7.0-7.2 (m, 4H); 7.6 (m, 2H).

Step D: Preparation of 4-[[4-(2,6-Dimethylbenzyloxy)-3-methoxy]phenyl]-4-oxobutyric acid:

10

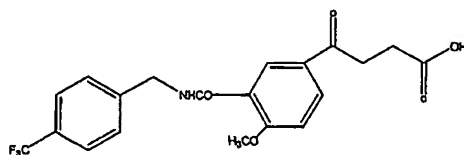
Using the method of Example 36, Step E, the title compound was obtained.

$^1\text{H}$  NMR (270 MHz,  $\text{CDCl}_3$ ): 2.4 (s, 6H); 2.8 (t, 2H); 3.3 (t, 2H); 3.9 (s, 3H); 5.1 (s, 2H); 7.0-7.2 (m, 4H); 7.6 (m, 2H).

15

EXAMPLE 47: Synthesis of 4-[5-[[N-(4-Trifluoromethylbenzyl)aminocarbonyl]-2-methoxy]phenyl]-4-oxobutyric acid:

20



Step A: Preparation of Methyl 2-methoxy-5-acetylbenzoate:

To a stirred solution of Methyl 2-hydroxy-5-acetylbenzoate (12 g, 61.7 mmol) in DMF (200 ml) was added cesium carbonate (24.15 g, 74.1 mmol) and MeI (9.64 g, 68 mmol).

25

The reaction mixture was stirred for 16 hours at  $0^\circ\text{C}$  and then diluted with ethyl acetate, washed with aq  $\text{Na}_2\text{S}_2\text{O}_5$ , brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated. The purification was done by flash chromatography on silica gel column (ethyl acetate: hexane 1:2) to provide the title compound as an off white solid.

30

<sup>1</sup>H NMR (270 MHz, DMSO): 2.6 (s, 3H); 3.8 (s, 3H); 3.9 (s, 3H); 7.3 (d, 1H); 8.1 (dd, 1H); 8.2 (s, 1H).

Step B: Preparation of 2-Methoxy-5-acetylbenzoic acid:

5

Methyl 2-methoxy-5-acetylbenzoate (Step A, 3 g, 14.4 mmol) was dissolved in acetic acid (80 ml) and then treated with c HCl (28 ml). The reaction mixture was refluxed for 4 hours, concentrated under reduced pressure and lyophilized to provide the title compound as cream color solid, which was used without further purification.

10

<sup>1</sup>H NMR (270 MHz, DMSO): 2.6 (s, 3H); 3.9 (s, 3H); 7.3 (d, 1H); 8.1 (dd, 1H); 8.2 (s, 1H).

Step C: Preparation of 5-Acetyl-2-methoxy-N-[[4-(trifluoromethyl)phenyl]methyl]

15

benzamide:

To a stirred solution of 2-Methoxy-5-acetylbenzoic acid (Step B, 2.5 g, 12.8 mmol), HOBt.H<sub>2</sub>O (2.08 g, 15.4 mmol), and EDC (3.70 g, 19.3 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 ml) and DMF (5 ml) was added 4-(Trifluoromethyl)benzylamine (2.48 g, 14.1 mmol), and the mixture was stirred for 16 hours at room temperature. The reaction mixture was concentrated under reduced pressure and then redissolved in ethyl acetate. The organic layer was washed with 3% K<sub>2</sub>CO<sub>3</sub>, 1 N HCl, and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The purification was done by flash chromatography on silica gel column (chloroform:methanol 95:5) to provide the title compound as white solid.

25

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 2.6 (s, 3H); 4.0 (s, 3H); 4.8 (d, 2H); 7.0 (d, 1H); 7.5 (d, 2H); 7.6 (d, 2H); 8.1 (dd, 1H); 8.8 (s, 1H).

Step D: Preparation of Ethyl 4-[5-[[N-(4-trifluoromethylbenzyl)aminocarbonyl]-2-

30

methoxy]phenyl]-4-oxobutyrates:

Using the method of Example 17, Step B, the title compound was obtained.

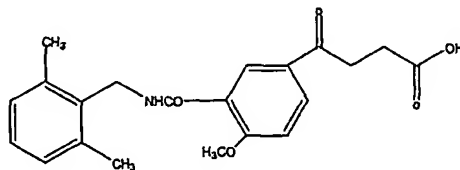
<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 1.2 (s, 3H); 2.6 (t, 2H); 3.3 (t, 2H); 4.0 (s, 3H); 4.4 (q, 2H); 4.8 (s, 2H); 7.0 (d, 1H); 7.4 (d, 2H); 7.6 (d, 2H); 8.1 (dd, 1H); 8.8 (s, 1H).

Step E: Preparation of 4-[5-[[N-(4-Trifluoromethylbenzyl)aminocarbonyl]-2-methoxy]phenyl]-4-oxobutyric acid:

Using the method of Example 36, Step E, the title compound was obtained.

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>: CD<sub>3</sub>OD): 2.6 (t, 2H); 3.3 (t, 2H); 4.0 (s, 3H); 4.7 (s, 2H); 7.0 (d, 1H); 7.4 (d, 2H); 7.6 (d, 2H); 8.1 (dd, 1H); 8.8 (s, 1H).

EXAMPLE 48: Synthesis of 4-[5-[[N-(2,6-Dimethylbenzyl)aminocarbonyl]-2-methoxy]phenyl]-4-oxobutyric acid:



Step A: Preparation of 2,6-Dimethylbenzyl Alcohol:

Using the method of Example 35, Step A, the title compound was obtained.

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 2.4 (s, 6H); 4.7 (s, 2H); 7.0-7.15 (m, 3H).

Step B: Preparation of N-(2,6-Dimethylbenzyl)phthalimide:

25

To a stirred solution of 2,6-Dimethylbenzyl Alcohol (Step A, 6.59 g, 48.4 mmol) in DMSO (20 ml) was added chlorotrimethylsilane (15.75 ml, 145 mmol) at room temperature, and the mixture was stirred for one hr. To this reaction mixture were added ethyl acetate and water, the organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give an oil. The oily residue was redissolved in DMF (100 ml) and potassium phthalimide (10.76 g, 58.1 mmol) was added. The

reaction mixture was stirred for 16 hours at room temperature, ethyl acetate was added, and the organic layer was washed with 3% Na<sub>2</sub>CO<sub>3</sub>, 1 N HCl, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give white solid. The purification was done by flash chromatography on silica gel column (chloroform: methanol 95:5) to provide the title  
5 compound as white solid.

<sup>1</sup>H NMR (270 MHz, DMSO): 2.3 (s, 6H); 4.8 (s, 2H); 7.0 (m, 3H); 7.8 (s, 4H).

Step C: Preparation of 2,6-Dimethylbenzyl Amine:

10 To a stirred solution of N- (2,6-Dimethylbenzyl)phthalimide (Step B, 7.77 g, 29.3 mmol) in ethanol (80 ml) was added hydrazine monohydrate (2.16 ml, 44.52 mmol) and the reaction mixture was refluxed for 3.5 hours. To this reaction mixture was added c HCl to bring pH to 1 and refluxing continued for another 3.5 hours, water was added and reaction mixture was filtered, the filtrate was concentrated and pH was adjusted to  
15 10 with 2 N NaOH. The residue was taken in methylene chloride and washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give an oil which was used without further purification.

<sup>1</sup>H NMR (270 MHz, DMSO): 2.3 (s, 6H); 3.8 (s, 2H); 7.0 (m, 3H).

20

Step D: Preparation of 5-Acetyl-2-methoxy-N-[[2,6-dimethyl)phenyl]methyl] benzamide:

To a stirred solution of 2-Methoxy-5-acetylbenzoic acid (Example 47, Step B, 2.5 g, 12.8 mmol), HOBt (2.08 g, 15.4 mmol), and EDC (3.70 g, 19.3 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20  
25 ml) and DMF (5 ml) was added 2,6-Dimethylbenzyl amine (Step C, 1.72 g, 12.8 mmol), and the mixture was stirred for 16 hours at room temperature. The reaction mixture was concentrated under reduced pressure and then redissolved in ethyl acetate. The organic layer was washed with 3% K<sub>2</sub>CO<sub>3</sub>, 1 N HCl, and brine, dried over Na<sub>2</sub>SO<sub>4</sub>,  
30 filtered and concentrated. The purification was done by flash chromatography on silica gel column (chloroform:methanol 95:5) to provide the title compound as white solid.

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 2.5 (s, 6H); 2.6 (s, 3H); 3.9 (s, 3H); 4.7 (s, 2H); 7.0 (d, 1H); 7.2 (m, 3H); 7.6 (br, 1H); 8.1 (dd, 1H); 8.8 (s, 1H).

Step E: Preparation of Ethyl 4-[5-[[N-(2,6-dimethylbenzyl)aminocarbonyl]-2-methoxy]phenyl]-4-oxobutyrate:

Using the method of Example 17, Step B, the title compound was obtained.

5

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 1.2 (t, 3H); 2.4 (s, 6H); 2.7 (t, 2H); 3.3 (t, 2H); 3.9 (s, 3H); 4.4 (q, 2H); 4.7 (s, 2H); 7.0 (m, 3H); 7.2 (m, 1H); 8.1 (dd, 1H); 8.7 (s, 1H).

Step F: Preparation of 4-[5-[[N-(2,6-Dimethylbenzyl)aminocarbonyl]-2-methoxy]phenyl]-4-oxobutyric acid:

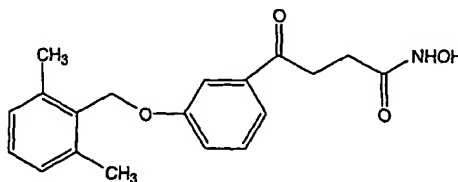
10

Using the method of Example 36, Step E, the title compound was obtained.

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>: CD<sub>3</sub>OD): 2.4 (s, 6H); 2.7 (t, 2H); 3.3 (t, 2H); 3.9 (s, 3H); 4.7 (s, 2H); 7.0 (m, 3H); 7.2 (m, 1H); 8.1 (dd, 1H); 8.7 (s, 1H).

15

EXAMPLE 49: Synthesis of 4-(3-(2,6-Dimethylbenzyloxy)phenyl)-4-oxobutanecarbohydroxamic acid:



20

Step A: Preparation of 2,6-Dimethylbenzyl Alcohol:

Using the method of Example 35, Step A, the title compound was obtained.

25 <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 2.4 (s, 6H); 4.7 (s, 2H); 7.0-7.15 (m, 3H).

Step B: Preparation of 3-(2,6-Dimethylbenzyloxy)acetophenone:

Using the method of Example 35, Step B, the title compound was obtained.

30



<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 2.4 (s, 6H); 2.6 (s, 3H); 5.1 (s, 2H); 7.1 (dd, 2H); 7.2 (m, 2H); 7.4 (t, 1H); 7.6 (m, 2H).

Step C: Preparation of Ethyl 4-(3-(2,6-dimethylbenzyloxy)phenyl)-4-oxobutyrates:

5

Using the method of Example 17, Step B, the title compound was obtained.

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 1.2 (s, 3H); 2.4 (s, 6H); 2.8 (t, 2H); 3.2 (t, 2H); 4.4 (q, 2H); 5.1 (s, 2H); 7.1 (d, 2H); 7.2 (m, 2H); 7.4 (t, 1H); 7.6 (m, 2H).

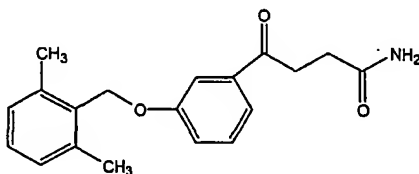
10

Step D: Preparation of 4-(3-(2,6-Dimethylbenzyloxy)phenyl)-4-oxobutanecarbohydroxamic acid:

To a hydroxylamine hydrochloride solution in dry ethanol, add a solution of potassium  
15 hydroxide in dry ethanol at 35°C. Cool the mix and add Ethyl 4-(3-(2,6-dimethylbenzyloxy)phenyl)-4-oxobutyrates (Step C), and powdered potassium hydroxide.

After few hours, reaction mixture can be diluted with water and neutralize with  
20 hydrochloric acid, filter and recrystallize to give title compound.

EXAMPLE 50: Synthesis of 4-(3-(2,6-Dimethylbenzyloxy)phenyl)-4-oxobutyramide:



25

Step A: Preparation of 2,6-Dimethylbenzyl Alcohol:

Using the method of Example 35, Step A, the title compound was obtained.

30 <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 2.4 (s, 6H); 4.7 (s, 2H); 7.0-7.15 (m, 3H).

Step B: Preparation of 3-(2,6-Dimethylbenzyloxy)acetophenone:

Using the method of Example 35, Step B, the title compound was obtained.

- 5 <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 2.4 (s, 6H); 2.6 (s, 3H); 5.1 (s, 2H); 7.1 (dd, 2H); 7.2 (m, 2H); 7.4 (t, 1H); 7.6 (m, 2H).

Step C: Preparation of Ethyl 4-(3-(2,6-dimethylbenzyloxy)phenyl)-4-oxobutyrates:

- 10 Using the method of Example 17, Step B, the title compound was obtained.

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 1.2 (s, 3H); 2.4 (s, 6H); 2.8 (t, 2H); 3.2 (t, 2H); 4.4 (q, 2H); 5.1 (s, 2H); 7.1 (d, 2H); 7.2 (m, 2H); 7.4 (t, 1H); 7.6 (m, 2H).

- 15 Step D: Preparation of 4-(3-(2,6-Dimethylbenzyloxy)phenyl)-4-oxobutyric acid:

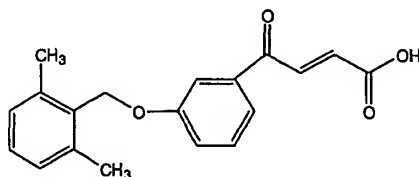
Using the method of Example 35, Step D, the title compound was obtained.

- 20 <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 2.4 (s, 6H); 2.8 (t, 2H); 3.3 (t, 2H); 5.1 (s, 2H); 7.1 (d, 2H); 7.2-7.3 (m, 2H); 7.4 (t, 1H); 7.6 (m, 2H).

Step E: Preparation of 4-(3-(2,6-Dimethylbenzyloxy)phenyl)-4-oxobutyramide:

- 25 To a solution of 4-(3-(2,6-Dimethylbenzyloxy)phenyl)-4-oxobutyric acid (Step D) in DMF, add triethylamine and BOP, after couple of hours of stirring, reaction mixture can be added to liquid ammonia at -40°C and the resulting mixture can be warmed for 16 hours to give title compound.

EXAMPLE 51: Synthesis of 4-(3-(2,6-Dimethylbenzyloxy)phenyl)-4-oxo-2-butenic acid:



5

Step A: Preparation of 2,6-Dimethylbenzyl Alcohol:

Using the method of Example 35, Step A, the title compound was obtained.

10  $^1\text{H}$  NMR (270 MHz,  $\text{CDCl}_3$ ): 2.4 (s, 6H); 4.7 (s, 2H); 7.0-7.15 (m, 3H).

Step B: Preparation of 3-(2,6-Dimethylbenzyloxy)acetophenone:

Using the method of Example 35, Step B, the title compound was obtained.

15

$^1\text{H}$  NMR (270 MHz,  $\text{CDCl}_3$ ): 2.4 (s, 6H); 2.6 (s, 3H); 5.1 (s, 2H); 7.1 (dd, 2H); 7.2 (m, 2H); 7.4 (t, 1H); 7.6 (m, 2H).

Step C: Preparation of Ethyl 4-(3-(2,6-dimethylbenzyloxy)phenyl)-4-oxobutyrate:

20

Using the method of Example 17, Step B, the title compound was obtained.

$^1\text{H}$  NMR (270 MHz,  $\text{CDCl}_3$ ): 1.2 (s, 3H); 2.4 (s, 6H); 2.8 (t, 2H); 3.2 (t, 2H); 4.4 (q, 2H); 5.1 (s, 2H); 7.1 (d, 2H); 7.2 (m, 2H); 7.4 (t, 1H); 7.6 (m, 2H).

25

Step D: Preparation of Ethyl 4-(3-(2,6-dimethylbenzyloxy)phenyl)-4-oxo-3-bromobutyrate:

To a ice cooled solution of Ethyl 4-(3-(2,6-dimethylbenzyloxy)phenyl)-4-oxobutyrate (Step C, 3 g, 9 mmol) in dry ether (70 ml) was added dropwise bromine (0.7971 g, 9.9 mmol) diluted in ether (30 ml). After 4 hours of stirring, reaction mixture was

30

concentrated and purified by flash chromatography on silica gel column (EtOAc: Hex, 1:4) to provide the title compound.

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 1.2 (s, 3H); 2.4 (s, 6H); 3.1 (m, 1H); 3.5 (m, 1H); 4.2 (q, 2H); 5.1 (s, 2H); 5.5 (m, 1H); 7.1 (d, 2H); 7.2 (m, 2H); 7.4 (t, 1H); 7.6 (m, 2H).

Step E: Preparation of Ethyl 4-(3-(2,6-dimethylbenzyloxy)phenyl)-4-oxo-2-butenate:

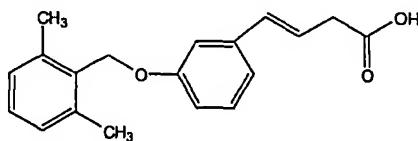
Triethylamine (5.95 g, 58.9 mmol) was added to a solution of Ethyl 4-(3-(2,6-dimethylbenzyloxy)phenyl)-4-oxo-3-bromo-butyrate (Step D, 2.47 g, 5.8 mmol) in carbon tetrachloride (50 ml). After stirring for 4 hours at room temperature, the reaction mixture was filtered through a pad of silica gel few times, and concentrated to give the title compound.

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 1.2 (s, 3H); 2.4 (s, 6H); 4.2 (q, 2H); 5.1 (s, 2H); 6.9 (dd, 1H); 7.1 (d, 2H); 7.2 (m, 2H); 7.4 (t, 1H); 7.6 (m, 2H); 7.9 (dd, 1H).

Step F: Preparation of 4-(3-(2,6-Dimethylbenzyloxy)phenyl)-4-oxo-2-butenic acid:

To a solution of Ethyl 4-(3-(2,6-dimethylbenzyloxy)phenyl)-4-oxo-2-butenate (Step E) in abs ethanol at low temp, add aqueous sodium hydroxide, after an hour, concentrate and purify by flash chromatography on silica gel column (chloroform:methanol 95:5 spiked with acetic acid).

EXAMPLE 52: Synthesis of 4-(3-(2,6-Dimethylbenzyloxy)phenyl)-3-butenic acid:



Step A: Preparation of 2,6-Dimethylbenzyl Alcohol:

Using the method of Example 35, Step A, the title compound was obtained.

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 2.4 (s, 6H); 4.7 (s, 2H); 7.0-7.15 (m, 3H).

Step B: Preparation of 3-(2,6-Dimethylbenzyloxy)acetophenone:

Using the method of Example 35, Step B, the title compound was obtained.

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 2.4 (s, 6H); 2.6 (s, 3H); 5.1 (s, 2H); 7.1 (dd, 2H); 7.2 (m,  
5 2H); 7.4 (t, 1H); 7.6 (m, 2H).

Step C: Preparation of Ethyl 4-(3-(2,6-dimethylbenzyloxy)phenyl)-4-oxobutyrate:

Using the method of Example 17, Step B, the title compound was obtained.

10

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 1.2 (s, 3H); 2.4 (s, 6H); 2.8 (t, 2H); 3.2 (t, 2H); 4.4 (q,  
2H); 5.1 (s, 2H); 7.1 (d, 2H); 7.2 (m, 2H); 7.4 (t, 1H); 7.6 (m, 2H).

Step D: Preparation of Ethyl 4-(3-(2,6-dimethylbenzyloxy)phenyl)-4-hydroxy-butyrate:

15

To a solution of Ethyl 4-(3-(2,6-dimethylbenzyloxy)phenyl)-4-oxobutyrate (Step C) in tetrahydrofuran, add sodium borohydride dissolved in water. After 3-4 hours of stirring at room temperature, quench with an acid. The organic layer can be taken in dichloromethane, wash with water, aqueous sodium bicarbonate, and brine, dry over  
20 Na<sub>2</sub>SO<sub>4</sub>, filter and concentrate. If needed, the compound can be purified by flash chromatography on silica gel column (EtOAc:Hex).

Step E: Preparation of Ethyl 4-(3-(2,6-dimethylbenzyloxy)phenyl)-4-bromo-butyrate:

25 To a solution of Ethyl 4-(3-(2,6-dimethylbenzyloxy)phenyl)-4-hydroxy-butyrate (Step D) in dioxane, add phosphorous tribromide in dioxane dropwise. After stirring at room temperature for 16 hours, quench with water and chloroform. After few minutes, the reaction mixture can be neutralized by mild aqueous base, dry organic layer over Na<sub>2</sub>SO<sub>4</sub>, filter, concentrate and purify by flash chromatography on silica gel column  
30 (EtOAc:hex).

Step F: Preparation of Ethyl 4-(3-(2,6-dimethylbenzyloxy)phenyl)-3-butenate:

Add Triethylamine to a solution of Ethyl 4-(3-(2,6-dimethylbenzyloxy)phenyl)-4-bromo-butyrate (Step E) in carbon tetrachloride. After stirring approximately for 4 hours, the mixture can be filtered through a pad of silica gel few times, and concentrate to give the title compound.

5

Step G: Preparation of 4-(3-(2,6-Dimethylbenzyloxy)phenyl)-3-butenic acid:

To a solution of Ethyl 4-(3-(2,6-dimethylbenzyloxy)phenyl)-3-butenate (Step F) in abs ethanol at low temp, add aqueous sodium hydroxide, after an hour, concentrate and  
10 purify by flash chromatography on silica gel column (chloroform:methanol 95:5 spiked with acetic acid).

#### BIOLOGICAL ACTIVITY EXAMPLES

15 EXAMPLE A. Compound AH improves metabolic abnormalities in insulin-dependent diabetes

Streptozotocin (STZ) is a toxin that selectively destroys insulin-producing pancreatic beta cells, and is widely used to induce insulin-dependent diabetes in experimental  
20 animals.

Female Balb/C mice (8 weeks old; 18-20 grams body weight) were treated with streptozotocin (STZ) (50 mg/kg i.p. on each of five consecutive days). Fourteen days after the last dose of STZ, blood glucose was measured to verify that the animals were  
25 diabetic, and the mice were divided into two groups of 5 animals each, one group receiving Compound AH (250 mg/kg) daily by oral gavage, and the other receiving vehicle (0.75% hydroxypropylmethylcellulose, a suspending agent, in water). A group of nondiabetic mice from the same cohort that did not receive STZ were also monitored. Blood samples were taken periodically for determination of blood glucose  
30 concentrations, and body weights were also recorded.

After several weeks of treatment, blood glucose concentrations in mice treated with oral Compound AH began to decrease toward baseline, whereas blood glucose in the vehicle-treated control animals continued to rise. Body weights and blood glucose,

triglyceride and cholesterol concentrations 14 weeks after the beginning of drug treatment are shown in Table 1.

Table 1 Serum chemistries and body weights in streptozotocin diabetic mice treated with oral Compound AH for 14 weeks

Group	Glucose mg/dL	Triglycerides mg/dL	Cholesterol mg/dL	Body Weight (g)
Nondiabetic + Vehicle	138 $\pm$ 6	88 $\pm$ 9	88 $\pm$ 6	21 $\pm$ 0.6
Diabetic + Vehicle	615 $\pm$ 46	154 $\pm$ 16	133 $\pm$ 6	17.5 $\pm$ 1.0
Diabetic + Compound AH	207 $\pm$ 12	62 $\pm$ 7*	82 $\pm$ 2 *	21.7 $\pm$ 0.8*

\* = significantly different from STZ Diabetic group, P<.001

Oral Compound AH treatment resulted in significant amelioration of metabolic abnormalities associated with insulin-dependent diabetes.

EXAMPLE B. Oral Compound AH improves survival of mice with lethal insulin-dependent diabetes

Female Balb/C mice (14 weeks old) were treated with a single dose of streptozotocin (175 mg/kg i.p.) to induce severe insulin-dependent diabetes. Seven days later, mice were divided into three treatment groups: Compound AH, pioglitazone, and vehicle. Mice were treated daily via oral gavage, and survival was monitored over time.

Table 2: Survival at 12 weeks

Groups	Survivors
Vehicle	0/5
Pioglitazone 30 mg/kg/day	2/5
Compound AH 250 mg/kg/day	4/5

All of the diabetic animals treated with oral vehicle died of severe, uncontrolled diabetes. Two of five animals treated with pioglitazone, an antidiabetic insulin sensitizer used to treat humans with noninsulin-dependent diabetes, were alive at 12 weeks, but had lost 15-20% of their body weight. Four of the five animals treated with oral Compound AH were alive at 12 weeks, and their body weights recovered and were maintained in the normal range.

EXAMPLE C: Oral Compound AA reduces mortality in severe insulin-dependent diabetes

Female balb/C mice (19 wks of age at start of experiment) were challenged with multiple high doses of STZ (75 mg/kg i.p. on 5 consecutive days). Animals were then divided in two groups (20 mice / group) matched for severity of diabetes. Four days after the last dose of STZ, treatments were initiated. One group received Vehicle (0.4 ml of 0.75% HPMC, p.o.), and the other group received oral COMPOUND AA (30 mg/kg/day). After three weeks of daily treatment, cumulative mortality in the Vehicle Control group was 19/20 mice. In contrast, only 5/20 of the COMPOUND AA mice died during this time.

EXAMPLE D: Compound AH reduces the incidence of spontaneous diabetes and mortality in NOD mice

A substantial proportion of NOD ("non-obese diabetic") mice develop insulin-dependent diabetes as a consequence of spontaneous autoimmune destruction of pancreatic islet cells. Two groups of 20 NOD mice (6 weeks old) were treated daily with either oral Vehicle (0.4 ml of 0.75% hydroxypropyl methylcellulose in water; HPMC) or Compound AH (200 mg/kg/day) suspended in HPMC. The incidence of mortality due to spontaneous development of severe insulin-dependent diabetes was monitored over a period of seven months. At the end of this time, 13/20 mice treated with vehicle had died of uncontrolled diabetes, whereas only 5/20 mice treated with Compound AH had died.



EXAMPLE E. Compound AW reduces hyperglycemia and hyperlipidemia, and ameliorates fatty liver disease in ob/ob obese diabetic mice

Ob/ob mice have a defect in the gene for leptin, a protein involved in appetite  
5 regulation and energy metabolism, and are hyperphagic, obese, and insulin resistant. They develop hyperglycemia and fatty liver.  
Male lean (ob/+ heterozygote) and obese (ob/ob homozygote) C57BL/6 mice approximately 8 weeks of age were obtained from Jackson Labs (Bar Harbor, ME) and randomly assigned into groups of 5 animals such that body weights and blood glucose  
10 concentrations were similar between groups. All animals were maintained under the control of temperature (23 C), relative humidity ( $50 \pm 5$  %) and light (7:00 – 19:00), and allowed free access to water and laboratory chow (Formulab Diet 5008, Quality Lab Products, Elkridge, MD). Blood glucose was routinely determined with glucose test strips and a Glucometer Elite XL device (Bayer Corporation). At selected time  
15 points, blood samples (~100 microliters) were obtained with a heparinized capillary tube via the retro-orbital sinus for serum chemistry analysis. Serum chemistry (glucose, triglycerides, cholesterol, BUN, creatinine, AST, ALT, SDH, CPK and free fatty acids) analyses were performed on a Hitachi 717 Analyzer, and plasma insulin and pancreatic insulin were measured by an electrochemiluminescent immunoassay (Origen  
20 Analyzer, Igen, Inc., Gaithersburg, MD).

Groups of ob/ob mice were divided into treatment cohorts as indicated below, and given daily oral doses of Compound AW (10, 30, 100, 150 or 300 mg), rosiglitazone (1, 3, 10 or 30 mg), or pioglitazone (30 or 100 mg). The latter two compounds are insulin-  
25 sensitizing drugs used in the treatment of human patients with non-insulin dependent diabetes mellitus, and are used as comparators for efficacy and safety of compounds of the invention. The dose ranges of compounds in this experiment were chosen to include both suboptimal and potentially supraoptimal doses.

30 Compound AW produced reduction in blood glucose comparable to that achieved with pioglitazone and rosiglitazone, as shown in Table 3. At doses of 100 to 300 mg/kg/day, Compound AW reduced serum triglycerides and fatty acids better than did either rosiglitazone or pioglitazone at their optimum antihyperglycemic doses.

Table 3 Effect of Compound AW, pioglitazone (PG) and rosiglitazone (RSG) on serum glucose, triglycerides, and free fatty acids in ob/ob mice

	Glucose $\pm$ SEM	Triglycerides $\pm$ SEM	Free Fatty Acids $\pm$ SEM
Group	mg/dL	mg/dL	micromoles/L
ob/+	268.6 $\pm$ 12.9	111.6 $\pm$ 12.0	2216 $\pm$ 197.4
ob/ob	384.2 $\pm$ 53.8	106.6 $\pm$ 2.909	3399 $\pm$ 345.6
AW-10	369.6 $\pm$ 62.5	115.6 $\pm$ 7.8	3697.4 $\pm$ 357.8
AW -30	280.2 $\pm$ 46.7	96.4 $\pm$ 7.3	2552.2 $\pm$ 334.7
AW -100	286 $\pm$ 47.1	66.2 $\pm$ 5.9	1476 $\pm$ 82.1
AW -150	188.6 $\pm$ 28.8	72.6 $\pm$ 5.6	1481 $\pm$ 158.8
AW -300	128.4 $\pm$ 8.8	63.6 $\pm$ 3.4	1452.6 $\pm$ 111.1
PG-30	188.2 $\pm$ 21.4	111.2 $\pm$ 7.5	2606 $\pm$ 139.2
PG-100	174.6 $\pm$ 11.5	95.2 $\pm$ 4.8	1983.4 $\pm$ 66.1
RSG-1	142.75 $\pm$ 8.8	109.75 $\pm$ 4.4	2090.75 $\pm$ 67.7
RSG-3	190.2 $\pm$ 12.7	107.8 $\pm$ 3.8	2317.6 $\pm$ 85.3
RSG-10	188.2 $\pm$ 21.4	111.2 $\pm$ 7.5	2606.4 $\pm$ 139.2
RSG-30	174.6 $\pm$ 11.5	95.2 $\pm$ 4.8	1983.4 $\pm$ 66.1

- 5 Ob/ob mice develop chronic inflammatory fatty liver disease and are considered to be an animal model for nonalcoholic steatohepatitis (NASH), a condition which can lead toward progressive cirrhosis and liver dysfunction. In NASH, fat accumulation increases the susceptibility of the liver to inflammatory injury. One characteristic sign of NASH in patients is, in the absence of viral infection or alcoholism, elevated levels
- 10 in serum of enzymes that are released from damaged hepatocytes, e.g. alanine aminotransferase (ALT), aspartate aminotransferase (AST), and sorbitol dehydrogenase (SDH). These enzymes are elevated in ob/ob mice as a consequence of fatty liver and secondary inflammation. In Table 4, ALT, AST, and SDH in serum samples from mice treated with Compound AW, pioglitazone, and rosiglitazone are shown, as are enzyme
- 15 levels in serum from normal lean mice and from diabetic control mice treated only with vehicle. ALT, AST and SDH are significantly elevated in obese diabetic ob/ob mice compared to lean mice. Compound AW treatment at doses ranging from 30 mg/kg/day to 300 mg/kg/day resulted in a dose-dependent decrease in serum liver enzymes. In contrast, pioglitazone (30 and 100 mg/kg/day) and rosiglitazone (1 to 30 mg/kg/day)
- 20 induced an elevation in ALT and AST and did not change SDH. The serum liver enzyme profiles correlated with liver histology. Vehicle-treated ob/ob obese diabetic

mice had marked fat accumulation in the liver in discrete intracellular droplets. Daily Compound AW treatment for 4 weeks caused a marked reduction in liver fat droplets, whereas neither pioglitazone nor rosiglitazone reduced the size or density of fat droplets in the hepatocytes.

- 5 Table 4: Effect of Compound AW, pioglitazone and rosiglitazone on serum enzyme indicators of liver injury

Group	ALT (U/L) $\pm$ SEM	AST (U/L) $\pm$ SEM	SDH (U/L) $\pm$ SEM
Lean	106.4 $\pm$ 16.3	25.6 $\pm$ 2.7	23.2 $\pm$ 4.5
Diabetic	447.2 $\pm$ 63.4	645.6 $\pm$ 104.8	745.8 $\pm$ 102.4
2022-10	483.8 $\pm$ 81.9	653.4 $\pm$ 104.8	626.8 $\pm$ 93.8
AW -30	320.2 $\pm$ 46.2	399.6 $\pm$ 74.4	333.0 $\pm$ 66.9
AW -100	202.8 $\pm$ 38.0	143.8 $\pm$ 30.4	121.2 $\pm$ 14.1
AW -150	149.2 $\pm$ 15.6	185.8 $\pm$ 26.0	166.2 $\pm$ 20.0
AW -300	188.2 $\pm$ 10.3	335.4 $\pm$ 44.8	207.0 $\pm$ 29.3
PG-30	713.6 $\pm$ 80.6	1024 $\pm$ 88.7	782.0 $\pm$ 70.6
PG-100	646.0 $\pm$ 56.1	901.0 $\pm$ 49.3	603.0 $\pm$ 27.3
RSG-1	668.8 $\pm$ 42.9	798.0 $\pm$ 73.8	644.5 $\pm$ 51.6
RSG-3	716.6 $\pm$ 56.6	853.8 $\pm$ 43.8	615.4 $\pm$ 38.6
RSG-10	713.6 $\pm$ 80.5	1024.0 $\pm$ 88.7	782.0 $\pm$ 70.6
RSG-30	646.0 $\pm$ 56.1	901.2 $\pm$ 49.3	603.0 $\pm$ 27.3

- 10 The ob/ob Mice gained body weight during the four week treatment period. As is shown in Table 5, pioglitazone and rosiglitazone exacerbated weight gain relative to vehicle-treated mice, whereas Compound AW induced a dose-dependent attenuation of weight gain.

Table 5: Effect of Compound AW, Pioglitazone and Rosiglitazone on body weight gain of ob/ob mice

Groups	Mean body weight gain (grams)
HPMC (Vehicle)	+7.4
AW-3 mg/kg/day	+7.3
AW-10 mg/kg/day	+6.7
AW-30 mg/kg/day	+6.4
AW-100 mg/kg/day	+3.4
AW-150 mg/kg/day	+4.6
AW-300 mg/kg/day	-0.7
PG – 30 mg/kg/day	+10.0
PG – 100 mg/kg/day	+13.6
RSG – 1 mg/kg/day	+8.2
RSG – 3 mg/kg/day	+8.5
RSG – 10 mg/kg/day	+11.0
RSG – 30 mg/kg/day	+12.0

5 EXAMPLE F: Acute hypoglycemic effects of compounds of the invention in diabetic mice: Experiment 1.

Compounds of the invention display acute antihyperglycemic activity in animals with non insulin-dependent diabetes.

10

Male ob/ob diabetic mice were randomized into groups of five animals each. Body weights were 50 –55 g and blood glucose was approximately 300 mg/dL in the fed state. A single oral dose of a test substance suspended in 0.5% carboxymethylcellulose vehicle was administered by gavage. Blood glucose was measured in blood droplets obtained by nicking a tail vein with a razor using glucometer test strips and a Glucometer Elite XL device (Bayer) at 0, 0.5, 2, 4, 6 and 18 hours after the initial dosing. A 10% reduction in blood glucose versus oral vehicle is considered a positive screening result. Blood glucose reductions were generally maximal at 6 hours after drug administration.

15

Table 6: Acute hypoglycemic effect of compounds of the invention in ob/ob obese diabetic mice

Treatment Group	Blood	% Reduction vs Control
	Glucose After 6 hours	
Vehicle	297 $\pm$ 35	0.0 $\pm$ 11.8
Compound AA	242 $\pm$ 25	-18.5 $\pm$ 8.4
Compound AB	181 $\pm$ 19	-39.1 $\pm$ 6.4
Compound AF	314 $\pm$ 32	-24.6 $\pm$ 7.7 *
Compound AG	222 $\pm$ 23	-25.3 $\pm$ 7.7
Compound AH	223 $\pm$ 11	-24.9 $\pm$ 3.7
Compound AI	255 $\pm$ 9	-14.1 $\pm$ 3.0
Compound AJ	190 $\pm$ 14	-36.0 $\pm$ 4.7
Compound AK	210 $\pm$ 10	-29.3 $\pm$ 3.4
Compound AL	168 $\pm$ 13	-43.4 $\pm$ 4.4

- 5 \* Initial blood glucose in this group was  $416 \pm 29$  mg/dL and the 6 hour reading is normalized to that initial value. In all other groups in this experiment, mean initial blood glucose was  $\leq 300$  mg/dL.

10 EXAMPLE G: Acute hypoglycemic effects of compounds of the invention in diabetic mice: Expt 2

Compounds of the invention display acute antihyperglycemic activity in animals with noninsulin-dependent diabetes.

- 15 Male ob/ob mice (50-55 grams; blood glucose  $\sim 300$  mg/dL) were divided into groups of five animals each, and given a single oral dose of test drug (250 mg/kg) suspended in 0.5% carboxymethylcellulose vehicle; a control group received oral vehicle alone. Six hours after oral administration of test drugs or vehicle (control), blood samples were obtained from a tail vein and glucose content was determined with a glucometer.

20

Table 7: Acute hypoglycemic effect of compounds of the invention in ob/ob obese diabetic mice

Treatment Group	Blood	
	Glucose	% Reduction vs
	after 6 hours	Control
	305 ± 20	
Vehicle Control	mg/dL	0.0 ± 5.0
Compound AN	152 ± 11	-50.2 ± 4.5 %
Compound AQ	220 ± 17	-27.9 ± 4.2 %
Compound AR	179 ± 14	-41.3 ± 4.2 %
Compound AS	167 ± 28	-45.2 ± 2.0 %
Compound AT	198 ± 28	-35.1 ± 2.3 %
Compound AU	224 ± 26	-26.6 ± 2.8 %
Compound AV	207 ± 23	-32.1 ± 3.0 %
Compound AW	143 ± 15	-53.1 ± 3.1 %
Compound AX	165 ± 23	-45.9 ± 2.4 %
Compound AY	185 ± 21	-39.3 ± 2.9 %
Compound AZ	186 ± 10	-39.0 ± 6.1 %

- 5 Oral treatment with compounds of the invention elicits an acute antihyperglycemic effect in obese diabetic mice.

#### EXAMPLE H: Antidiabetic effects of compounds of the invention in db/db mice

- 10 Db/db mice have a defect in leptin signaling, leading to hyperphagia, obesity and diabetes. Moreover, unlike ob/ob mice which have relatively robust islets, their insulin-producing pancreatic islet cells undergo failure during chronic hyperglycemia, so that they transition from hyperinsulinemia (associated with peripheral insulin resistance) to hypoinsulinemic diabetes.

15

Male db/db mice were given daily oral treatments with vehicle (0.75% hydroxypropylmethylcellulose) or antidiabetic compounds as indicated below. Blood samples were obtained via the retro-orbital sinus for serum chemistry analysis, or via the tail vein for glucose measurement with a test strip and glucometer.

20

After four weeks of daily oral dosing, Compound AW and Compound BH elicited a significant reduction in blood glucose. While pioglitazone did initially reduce blood glucose over the first 3 weeks, its activity had largely failed at the 4 week time point and thereafter. The dose of pioglitazone used in this experiment was reported in the literature to be a maximally-effective dose for treatment of db/db mice (Shimaya et al. (2000), Metabolism 49:411-7).

Table 8

Groups	Glucose mg/dL	Glucose (% of Control)
Vehicle (Control)	562 ± 24	100 ± 4
Compound AW – 150 mg/kg	313 ± 34 *	56 ± 6 *
Compound BH – 150 mg/kg	229 ± 49 *	41 ± 9 *
Pioglitazone – 100 mg/kg	558 ± 28	99 ± 5

\* Less than Vehicle Control value,  $p < .05$

In a second experiment in db/db mice, antidiabetic activity of Compound BI was compared with that of rosiglitazone. After 8 weeks of treatment, blood glucose and triglycerides were significantly lower in animals treated with either Compound BI or rosiglitazone, compared to vehicle-treated controls. The rosiglitazone dose used in this study was reported in published literature as the optimum dose for late stage db/db mice (Lenhard et al., (1999) Diabetologia 42:545-54). Groups consisted of 6-8 mice each.

Table 9

Groups	Glucose (mg/dL)	Triglycerides (mg/dL)
Vehicle (Control)	686 ± 47	147 ± 13
Rosiglitazone – 20mg/kg	343 ± 38 *	89 ± 16 *
Compound BI – 150 mg/kg	254 ± 30 *	99 ± 8 *

\* = Less than Vehicle Control value,  $P < .05$  (One-way ANOVA)

EXAMPLE I: Antidiabetic effects of compounds of the invention in db/db mice.

db/db mice have a defect in leptin signaling, leading to hyperphagia, obesity and diabetes. Moreover, unlike ob/ob mice on a C57BL/6J background, db/db mice on a  
5 C57BL/KS background undergo failure of their insulin-producing pancreatic islet  $\beta$  cells, resulting in progression from hyperinsulinemia (associated with peripheral insulin resistance) to hypoinsulinemic diabetes.

Male obese (db/db homozygote) C57BL/Ksola mice approximately 8 weeks of age,  
10 were obtained from Jackson Labs (Bar Harbor, ME) and randomly assigned into groups of 5 – 7 animals such that the body weights (50 – 55 g) and serum glucose levels ( $\geq 300$  mg/dl in fed state) were similar between groups; male lean (db/+ heterozygote) mice served as cohort controls. A minimum of 7 days was allowed for adaptation after arrival. All animals were maintained under controlled temperature (23 °C), relative  
15 humidity ( $50 \pm 5$  %) and light (7:00 – 19:00), and allowed free access to standard chow (Formulab Diet 5008, Quality Lab Products, Elkridge, MD) and water.

Treatment cohorts were given daily oral doses of (1% hydroxypropylmethylcellulose), Compounds BI, BO, BP, BQ or BR for 2 weeks. At the end of the treatment period 100  $\mu$ l of venous blood was withdrawn in a heparinized capillary tube from the retro-orbital  
20 sinus of db/db mice for serum chemistry analysis.

Effects of compounds of the invention on nonfasting blood glucose are shown in Table 10; effects on serum triglycerides and free fatty acids are shown in Table 11.



Table 10: The effects of Compounds BI, BO, BP, BQ or BR on blood glucose in the db/db mouse model

Groups	Glucose mg/dL	Glucose (% of Control)
Vehicle (Control)	632 ± 19	100 ± 3
BI – 150 mg/kg	279 ± 35 *	44 ± 6 *
BI – 100 mg/kg	423 ± 53 *	67 ± 8 *
BO – 100 mg/kg	586 ± 58	93 ± 9
BP – 100 mg/kg	629 ± 86	99 ± 14
BQ – 100 mg/kg	473 ± 49*	75 ± 7*
BR – 82 mg/kg	703 ± 64	111 ± 10

Blood glucose levels in lean, nondiabetic db/+ heterozygote mice were 225 ± 15 mg/dL

5

Table 11: Effect of Compounds BI, BO, BP, BQ or BR on serum glucose, triglycerides, and free fatty acids in db/db mice

Group	Triglycerides ± SEM (mg/dL)	Free Fatty Acids ± SEM (μM)
Lean	142.4 ± 6.3	2577.6 ± 80.8
Diabetic	444.3 ± 57.3	4044.9 ± 158.5
BI-150	103.6 ± 8.3	2234.0 ± 162.6
BI-100	134.0 ± 13.1	2999.9 ± 98.7
BO-100	261.1 ± 24.3	3766.3 ± 234.5
BP-100	302.1 ± 28.1	3772.6 ± 182.5
BQ-100	131.6 ± 20.7	2825.9 ± 110.9
BR-82	253.0 ± 32.0	3653.4 ± 207.5

10

EXAMPLE J: Antidiabetic effects of compounds of the invention in db/db mice.

db/db mice have a defect in leptin signaling, leading to hyperphagia, obesity and diabetes. Moreover, unlike ob/ob mice on a C57BL/6J background, db/db mice on a  
5 C57BL/KS background undergo failure of their insulin-producing pancreatic islet cells, resulting in progression from hyperinsulinemia (associated with peripheral insulin resistance) to hypoinsulinemic diabetes.

Male obese (db/db homozygote) C57BL/Ksola mice approximately 8 weeks of age,  
10 were obtained from Jackson Labs (Bar Harbor, ME) and randomly assigned into groups of 5 – 7 animals such that the body weights (50 –55 g) and serum glucose levels ( $\geq 300$  mg/dl in fed state) were similar between groups; male lean (db/+ heterozygote) mice served as cohort controls. A minimum of 7 days was allowed for adaptation after arrival. All animals were maintained under controlled temperature (23 °C), relative  
15 humidity ( $50 \pm 5$  %) and light (7:00 – 19:00), and allowed free access to standard chow (Formulab Diet 5008, Quality Lab Products, Elkridge, MD) and water.

Treatment cohorts were given daily oral doses of Vehicle (1% hydroxypropylmethylcellulose), Compounds BI, BS, BT, BU, BV or Fenofibrate for 2  
20 weeks. At the end of the treatment period 100  $\mu$ l of venous blood was withdrawn in a heparinized capillary tube from the retro-orbital sinus of db/db mice for serum chemistry analysis.

Effects of compounds of the invention on nonfasting blood glucose are shown in Table  
25 12; effects on serum triglycerides and free fatty acids are shown in Table 13.

Table 12: The effects of compounds BI, BS, BT, BU, BV and fenofibrate in db/db mice

Groups	Glucose mg/dL	Glucose (% of Control)
Vehicle (Control)	692.5 ± 55.4	100 ± 8
BI – 100 mg/kg	347.0 ± 43.1*	50 ± 6 *
BS– 93 mg/kg	372.0 ± 53.8*	54 ± 8 *
BT – 107 mg/kg	684.3 ± 63.6	99 ± 9
BU – 128 mg/kg	533.3 ± 46.7	77 ± 7
BV – 115 mg/kg	789.5 ± 38.9	114 ± 6
Fenofibrate – 113 mg/kg	563.2 ± 49.0	81 ± 7

Blood glucose levels in lean, nondiabetic db/+ heterozygote mice were 208.5 ± 6.6 mg/dL

5

Table 13: Effect of compounds BI, BS, BT, BU, BV and Fenofibrate on serum triglycerides and free fatty acids in db/db mice

Group	Triglycerides ± SEM (mg/dL)	Free Fatty Acids ± SEM (μM)
Lean	114.2 ± 8.7	2315.8 ± 238.3
Vehicle	232.8 ± 20.7	3511.8 ± 257.6
BI	77.8 ± 5.3	1997.2 ± 196.4
BS	132.0 ± 15.2	2867.4 ± 267.7
BT	211.5 ± 21.5	3897.7 ± 291.3
BU	172.5 ± 9.9	3587.0 ± 156.3
BV	153.2 ± 14.2	3373.8 ± 233.6
Fenofibrate	109.3 ± 9.1	3318.5 ± 208.7

#### 10 EXAMPLE K: Attenuation of cataractogenesis of compounds of the invention in Zucker diabetic fatty (ZDF) rats

Cataracts are one of the leading causes of progressive vision decline and blindness associated with ageing and diabetes, and the Zucker diabetic fatty (ZDF) model has  
 15 many similarities with human cataractogenesis, including biochemical changes and

oxidative stress in the lens. These rats, however, undergo cataractogenesis typically between 14 –16 weeks of age.

- Male ZDF rats and their aged-match Zucker lean (ZL) counterparts (fa/+ or +/+) were  
5 obtained from Genetic Models, Inc. (Indianapolis, IN) aged 12 weeks and acclimatized  
for 1 week prior to study. All animals were maintained under controlled temperature  
(23 °C), relative humidity ( $50 \pm 5$  %) and light (7:00 – 19:00), and allowed free access  
to standard chow (Formulab Diet 5008, Quality Lab Products, Elkridge, MD) and tap  
water ad libitum. Treatment cohorts were given a daily oral dose of vehicle and 100  
10 mg/kg of BI or BH for 10 weeks. Body weights and blood glucose were routinely  
determined (once a week, usually around 10:00 A.M.) from tail bleeds with glucose test  
strips and a Glucometer Elite XL device (Bayer Corporation). At the end of the  
treatment period 100  $\mu$ l of venous blood was collected (usually 10:00 A.M.) in a  
heparinized tube from the tail vein for serum chemistry analysis (Anilytics, Inc.,  
15 Gaithersburg, MD). Serum chemistry (glucose (GL), triglycerides (TG), aspartate  
aminotransferase (AST), alanine aminotransferase (ALT), sorbitol dehydrogenase  
(SDH), and free fatty acids (FFA)) analyses were performed on a Hitachi 717 Analyzer  
(Anilytics, Inc., Gaithersburg, MD). Plasma insulin was measured by an  
electrochemiluminescent immunoassay, ECL (Origen Analyzer, Igen, Inc.,  
20 Gaithersburg, MD). The animals were sacrificed and tissues and/or organs (lens and  
liver) were extirpated, weighed (wet weight) and processed for biochemical analyses.  
Malondialdehyde (MDA), a major product of lipid peroxidation was assayed in lenses  
according to Ohkawa et al (1979), Analytical Biochem 95, 351-358).
- 25 Table 14 shows the incidence of visible cataracts in the eyes of the ZDF rats. Table 15  
indicates additional quantitative indices of cataractogenesis in the same animals.

Table 14: Attenuation of cataractogenesis by Compounds BH and BI in ZDF rats.

5	Animal Groups	N	Cataract Formation		% Protection	
			Left Eye	Right Eye	Left Eye	Right Eye
	Vehicle-Control	6	6/6	6/6	0	0
	BI	6	3/6	1/6	50	83
10	BH	6	4/6	5/6	33	17
	Lean	4	0/4	0/4	N/A	N/A

Table 15: Attenuation of cataractogenesis by BH and BI in ZDF rats.

20	Groups	Weight (mg)		Size (mm)		Lenticular MDA
		Left Lens	Right Lens	Left Lens	Right Lens	nmol/g lens
	LEAN	51.2 ± 3.5	59.0 ± 0.4	3.8 ± 0.2	3.9 ± 0.1	0.4 ± 0.0
	Vehicle	15.1 ± 1.4	16.8 ± 1.7	1.9 ± 0.1	2.0 ± 0.2	2.4 ± 0.2
25	BI	38.1 ± 7.3**	54.9 ± 1.2*	3.4 ± 0.2*	3.8 ± 0.1*	0.8 ± 0.1‡
	BH	27.0 ± 7.2	20.0 ± 6.6	2.5 ± 0.3	2.1 ± 0.4	1.9 ± 0.2

30 Data are means ± SEM. \*p < 0.05 compared with the vehicle-controls (diabetic) and Compound BH-treated groups, respectively; \*\*p < 0.05 compared with vehicle-controls; ‡p < 0.05 compared with vehicle-controls and Compound BH right lenses, respectively (One Way ANOVA, Tukey Test) All pairwise Multiple Comparison.

35 EXAMPLE L: Oral BI and BL lower circulating triglycerides, free fatty acids, insulin and leptin in high fat-fed C57Bl/6J mice

40 The high fat-fed mouse is a model for the hypertriglyceridemia and high circulating fatty acid levels, and the insulin and leptin resistance that are found in people at risk for and with obesity, diabetes, cardiovascular disease and other disorders. Male C57Bl/6J mice, approximately 8 weeks of age, were randomly assigned into groups of 6 animals. They were maintained under controlled temperature (23 °C), relative humidity (50 ± 5 %) and light (7:00 – 19:00), and allowed free access to food and water ad libitum. Mice were fed a high-fat diet (diet number D12451, containing 45% of calories as fat

(Research Diets, New Brunswick, NJ)) for 6 weeks. After the 6 weeks, groups of mice received either vehicle (hydroxymethylcellulose), BI, BL, Wy14,643 or rosiglitazone by oral gavage at the indicated doses for an additional 4 weeks while continuing on the high-fat diet. Plasma chemistries (Anilytics, Inc., Gaithersburg, MD) were assayed after 2 weeks of drug treatments. Plasma serum insulin (Figure 1) and leptin (Figure 2) were measured by an electrochemiluminescent immunoassay (Origen Analyzer, Igen, Inc., Gaithersburg, MD) after 4 weeks of drug treatments.

BI and BL were effective at lowering serum triglycerides and free fatty acids as well as insulin and leptin serum levels. Serum values from mice from the same cohort ("lean controls") that were maintained on regular lab chow (Formulab Diet 5008, Quality Lab Products, Elkridge, MD) are shown for comparison.

Table 16:

	Triglycerides (mg/dL)	Free Fatty Acids (umol/L)
Vehicle	135 ± 40.1	1686 ± 359.3
BI (10 mg/kg)	68.8 ± 5.7	1227 ± 193.7
“ (30 mg/kg)	66.5 ± 14.7	1292 ± 231.4
“ (100 mg/kg)	37.4 ± 8.3	992.8 ± 172.1
BL (10 mg/kg)	80 ± 12.2	1571.8 ± 100.9
“ (30 mg/kg)	66.4 ± 13.7	1413.2 ± 228.7
“ (100 mg/kg)	41 ± 5.6	1133.5 ± 132.7
Rosiglitazone (1 mg/kg)	76.6 ± 16.5	1537 ± 256.3
“ (3 mg/kg)	103.2 ± 10.8	1833.2 ± 169.8
“ (10 mg/kg)	129.5 ± 48.7	1810.3 ± 595
“ (100 mg/kg)	88 ± 7.2	1568.5 ± 197
Wy14643 (10 mg/kg)	70.6 ± 10.8	1512.2 ± 172.9
“ (30 mg/kg)	88 ± 12.5	1676 ± 237
“ (100 mg/kg)	88.4 ± 18.8	1839.8 ± 154.8
Rosi (3 mg/kg) + Wy14643 (100 mg/kg)	54.3 ± 10.5	1649.7 ± 260.5

EXAMPLE M: Oral BI lowers circulating triglycerides, free fatty acids, insulin and leptin in high fat-fed Sprague Dawley rats

The high fat-fed rat is a model for insulin and leptin resistance. Sprague-Dawley rats have an intact leptin system and respond to a high fat diet with hyperinsulinemia due to a downregulation of the normal insulin response in peripheral tissues such as liver, adipose tissue and muscle

Male Sprague-Dawley rats, approximately 17 weeks of age, were obtained from Jackson Labs (Bar Harbor, ME) and randomly assigned into groups of 5 – 7 animals; the body weights were similar between groups. All animals were maintained in a temperature-controlled (25°C) facility with a strict 12 h light/dark cycle and were given free access to water and food. Rats were fed a high-fat diet (diet number D12451 (containing 45 % of calories as fat), Research Diets, New Brunswick, NJ) for one month prior to drug treatment.

Groups of 6 Sprague-Dawley rats were treated with a single daily dose of vehicle (hydroxymethylcellulose), BI (10, 30 and 100 mg/kg), or rosiglitazone (3 mg/kg) for 6 weeks while maintaining the high-fat diet. At the indicated time points, blood samples (~100 µl) were obtained via the tail vein for serum chemistry analysis.

BI (30 mg/kg) reduced serum insulin, triglycerides; BI at all doses reduced free fatty acids.

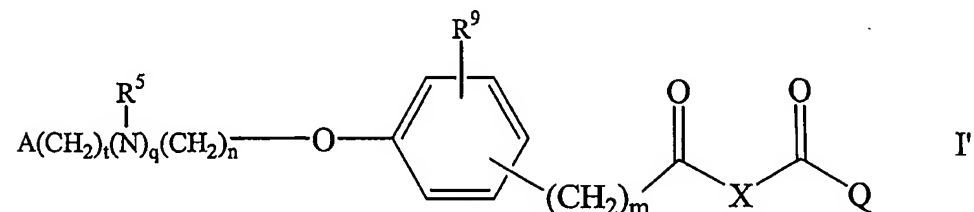
Table 17: Effect of BI and rosiglitazone on serum glucose, insulin, triglycerides and free fatty acids in high-fat fed Sprague-Dawley rats

	Group	Glucose (mg/dL)	Insulin (ng/ml)	Triglycerides (mg/dL)	Free Fatty Acids (µMol/L)
30	Lean	123.8 ± 7.0	0.72 ± 0.1	179.0 ± 72.3	743.5 ± 57.4
	Vehicle	122.3 ± 5.9	1.78 ± 0.3	200.7 ± 39.2	942.5 ± 181.0
35	BI-10	117.3 ± 8.8	2.18 ± 0.9	183.7 ± 58.4	923.7 ± 161.3
	BI-30	127.3 ± 22.2	1.46 ± 0.2	129.3 ± 20.0	738.7 ± 50.0
	BI-100	19.3 ± 3.5	1.79 ± 0.2	171.7 ± 33.1	725.7 ± 87.5
	RG-3	119.8 ± 5.4	1.57 ± 0.2	134.2 ± 15.2	758.8 ± 61.0

## CLAIMS

What is claimed is:

1. A biologically active agent, wherein the agent is a compound of the formula:



wherein

n is 1 or 2;

m is 0 or 1;

q is 0 or 1;

t is 0 or 1;

R<sup>5</sup> is alkyl having from 1 to 3 carbon atoms;

R<sup>9</sup> is hydrogen, halo, or alkoxy having from 1 to 3 carbon atoms;

A is phenyl, unsubstituted or substituted by 1 or 2 groups selected from:  
halo, alkyl having 1 or 2 carbon atoms, perfluoromethyl, alkoxy having 1 or 2 carbon atoms, and perfluoromethoxy; or  
cycloalkyl having from 3 to 6 ring carbon atoms wherein the cycloalkyl is unsubstituted or one or two ring carbons are independently mono-substituted by methyl or ethyl; or

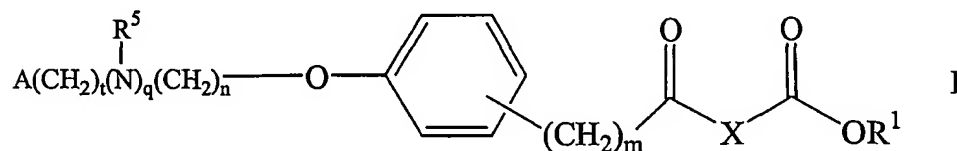


a 5 or 6 membered heteroaromatic ring having 1 or 2 ring heteroatoms selected from N, S and O and the heteroaromatic ring is covalently bound to the remainder of the compound of formula I by a ring carbon; and

X is  $-\text{CH}_2-$ , Q is  $-\text{OR}^1$  and  $\text{R}^1$  is ethyl; or X is  $-\text{CH}_2\text{CR}^{12}\text{R}^{13}-$  or  $-\text{CH}_2\text{CH}(\text{NHAc})-$  wherein each of  $\text{R}^{12}$  and  $\text{R}^{13}$  is independently hydrogen or methyl, Q is  $\text{OR}^1$  and  $\text{R}^1$  is hydrogen or alkyl having from 1 to 7 carbon atoms; or X is  $-\text{CH}_2\text{CH}_2-$  and Q is  $\text{NR}^{10}\text{R}^{11}$  wherein one of  $\text{R}^{10}$  and  $\text{R}^{11}$  is hydrogen, alkyl having from 1 to 3 carbon atoms or hydroxy, and the other is hydrogen or alkyl having from 1 to 3 carbon atoms;

or when  $\text{R}^1$  is hydrogen, a pharmaceutically acceptable salt of the compound.

2. The biologically active agent of claim 1, wherein the agent is a compound of the formula:



wherein

n is 1 or 2;

m is 0 or 1;

q is 0 or 1;

t is 0 or 1;

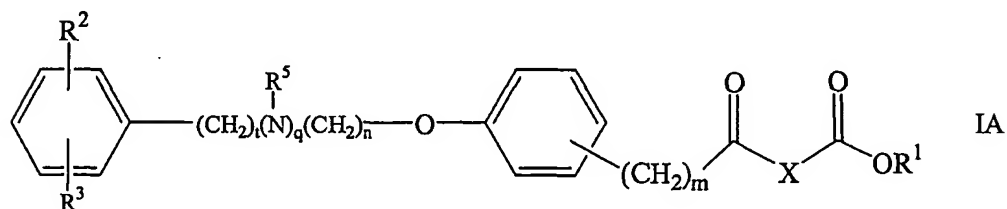
$\text{R}^5$  is alkyl having from 1 to 3 carbon atoms;

- A is phenyl, unsubstituted or substituted by 1 or 2 groups selected from: halo, alkyl having 1 or 2 carbon atoms, perfluoromethyl, alkoxy having 1 or 2 carbon atoms, and perfluoromethoxy; or cycloalkyl having from 3 to 6 ring carbon atoms wherein the cycloalkyl is unsubstituted or one or two ring carbons are independently mono-substituted by methyl or ethyl; or a 5 or 6 membered heteroaromatic ring having 1 or 2 ring heteroatoms selected from N, S and O and the heteroaromatic ring is covalently bound to the remainder of the compound of formula I by a ring carbon; and
- X is  $-\text{CH}_2-$  and  $\text{R}^1$  is ethyl; or X is  $-\text{CH}_2\text{CH}_2-$  or  $-\text{CH}_2\text{CH}(\text{NHAc})-$  and  $\text{R}^1$  is hydrogen or alkyl having from 1 to 7 carbon atoms;

or when  $\text{R}^1$  is hydrogen, a pharmaceutically acceptable salt of the compound.

3. The agent of claim 2, wherein  $\text{R}^1$  is hydrogen or ethyl.
4. The agent of claim 2, wherein q is 0.
5. The agent of claim 2, wherein X is  $-\text{CH}_2\text{CH}_2-$ .
6. The agent of claim 2, wherein A is phenyl, unsubstituted or substituted by 1 or 2 groups selected from: halo, alkyl having 1 or 2 carbon atoms, perfluoromethyl, alkoxy having 1 or 2 carbon atoms, and perfluoromethoxy.
7. The agent of claim 6, wherein each halo is independently fluoro or chloro.
8. The agent of claim 7, wherein each halo substituent on phenyl ring A is fluoro.
9. The agent of claim 8, wherein phenyl ring A is substituted by 2 fluoro groups.

10. The agent of claim 6, wherein the alkyl or alkoxy has 1 carbon atom.
11. The agent of claim 2, wherein A is cycloalkyl having from 3 to 6 ring carbon atoms wherein the cycloalkyl is unsubstituted or one or two ring carbons are independently mono-substituted by methyl or ethyl.
12. The agent of claim 11, wherein the cycloalkyl is unsubstituted or one or both ring carbons adjacent to the ring carbon covalently bound to the remainder of the compound of formula I are independently mono-substituted by methyl or ethyl.
13. The agent of claim 12, wherein A is unsubstituted cyclopropyl.
14. The agent of claim 2, wherein q is 1 and R<sup>5</sup> is methyl.
15. The biologically active agent of claim 2, wherein the agent is a compound of the formula:



wherein

n is 1 or 2;

m is 0 or 1;

q is 0 or 1;

t is 0 or 1;

R<sup>2</sup> and R<sup>3</sup> are each independently selected from hydrogen, halo, alkyl having 1 or 2 carbon atoms, perfluoromethyl, alkoxy having 1 or 2 carbon atoms, and perfluoromethoxy;

R<sup>5</sup> is alkyl having from 1 to 3 carbon atoms; and

X is -CH<sub>2</sub>- and R<sup>1</sup> is ethyl; or X is -CH<sub>2</sub>CH<sub>2</sub>- or -CH<sub>2</sub>CH(NHAc)- and R<sup>1</sup> is hydrogen or alkyl having from 1 to 7 carbon atoms;

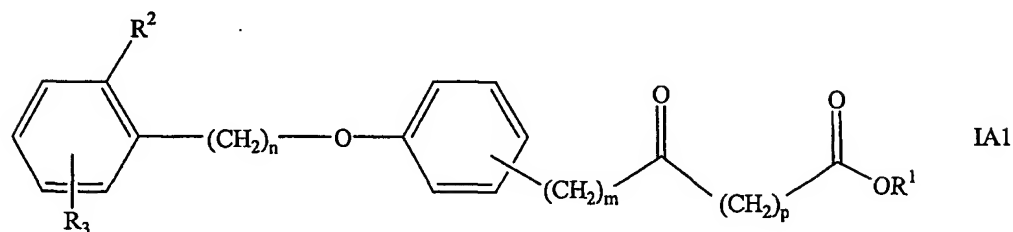
or when R<sup>1</sup> is hydrogen, a pharmaceutically acceptable salt of the compound.

16. The agent of claim 15, wherein R<sup>1</sup> is hydrogen or ethyl.

17. The agent of claim 16, wherein the compound is 4-[4-(2-(N-(2-fluorobenzyl)-N-methylamino)ethoxy)phenyl)]-4-oxobutyric acid.

18. The agent of claim 16, wherein the compound is (2RS) 2-(N-acetyl)-4-(4-(2,6-difluorobenzyloxy)phenyl)-4-oxobutyric acid.

19. The agent of claim 16, wherein the compound is 4-(3-(4-trifluoromethylbenzyloxy)phenyl)-4-oxobutyric acid.
20. The biologically active agent of claim 15, wherein the agent is a compound of the formula:



wherein

n is 1 or 2;

m is 0 or 1;

p is 1 and R<sup>1</sup> is ethyl; or p is 2 and R<sup>1</sup> is hydrogen or alkyl having from 1 to 7 carbon atoms;

R<sup>2</sup> and R<sup>3</sup> are each independently selected from hydrogen, halo, alkyl having 1 or 2 carbon atoms, perfluoromethyl, alkoxy having 1 or 2 carbon atoms, and perfluoromethoxy;

or when R<sup>1</sup> is hydrogen, a pharmaceutically acceptable salt of the compound.

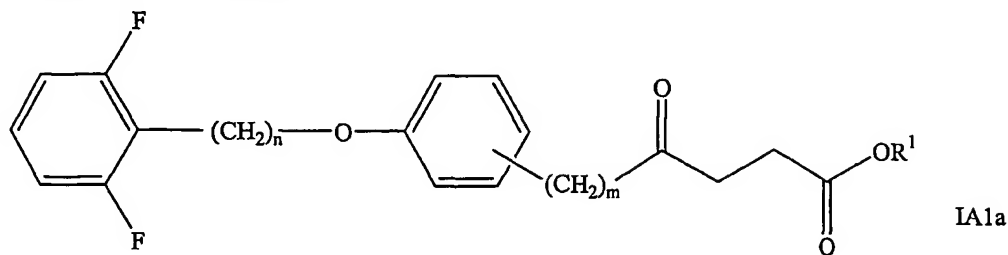
21. The agent of claim 20, wherein R<sup>1</sup> is hydrogen or ethyl.

22. The agent of claim 21, wherein the compound is 4-(3-(2,6-Dimethoxybenzyloxy)phenyl)-4-oxobutyric acid.

23. The agent of claim 20, wherein one of  $R^2$  and  $R^3$  is hydrogen or halo and the other is halo.
24. The agent of claim 23, wherein the compound is 4-(4-(3-fluorobenzoyloxy)phenyl)-4-oxobutyric acid.
25. The agent of claim 23, wherein the compound is 4-(4-(4-fluorobenzoyloxy)phenyl)-4-oxobutyric acid.
26. The agent of claim 23, wherein the compound is 4-(4-(2-chlorobenzoyloxy)phenyl)-4-oxobutyric acid.
27. The agent of claim 23, wherein  $R^2$  is fluoro and  $R^3$  is hydrogen.
28. The agent of claim 27, wherein the compound is 4-(4-(2-fluorobenzoyloxy)phenyl)-4-oxobutyric acid.
29. The agent of claim 27, wherein the compound is 4-(4-(2-(2-fluorophenyl)ethoxy)phenyl)-4-oxobutyric acid.
30. The agent of claim 27, wherein the compound is ethyl 4-(4-(2-fluorobenzoyloxy)phenyl)-4-oxobutyrate
31. The agent of claim 27, wherein the compound is ethyl 4-(3-(2-fluorobenzoyloxy)phenyl)-4-oxobutyrate.
32. The agent of claim 21, wherein  $R^2$  is fluoro and  $R^3$  is fluoro.
33. The agent of claim 32, wherein the compound is 4-(4-(2,5-difluorobenzoyloxy)phenyl)-4-oxobutyric acid.
34. The agent of claim 32, wherein the compound is 4-(4-(2,4-difluorobenzoyloxy)phenyl)-4-oxobutyric acid.

35. The agent of claim 32, wherein the compound is Ethyl 4-(4-(2,6-difluorobenzyloxy)phenyl)methyl-3-oxobutyrate.
36. The agent of claim 21, wherein  $R^2$  is methyl.
37. The agent of claim 36, wherein the compound is 4-(3-(2-Fluoro-6-methylbenzyloxy)phenyl)-4-oxobutyric acid.
38. The agent of claim 36, wherein the compound is Ethyl 4-(3-(2,6-dimethylbenzyloxy)phenyl)-4-oxobutyrate.
39. The agent of claim 36, wherein the compound is -(4-(2,6-dimethylbenzyloxy)phenyl)-4-oxobutyric acid.
40. The agent of claim 2, wherein the compound is 4-(3-((Cyclobutyl)methoxy)phenyl)-4-oxobutyric acid.
41. The agent of claim 1, wherein A is 2,6 -dimethylphenyl; t is 0, q is 0, n is 1, m is 0, x is  $-\text{CH}_2\text{CR}^{12}\text{R}^{13}$ -,  $\text{R}^{12}$  is hydrogen and  $\text{R}^{13}$  is hydrogen.
42. The agent of claim 41, wherein the compound is 4-(3-(2,6-dimethylbenzyloxy)phenyl)-4-oxo-2,2-dimethylbutyric acid.
43. The agent of claim 41, wherein the compound is 4-[[4-(2,6-dimethylbenzyloxy)-3-methoxy]phenyl]-4-oxobutyric acid.
44. The agent of claim 1, wherein the compound is 4-(3-(2,6-Dimethylbenzyloxy)phenyl)-4-oxobutanecarbohydroxamic acid.
45. The agent of claim 1, wherein the compound is -(3-(2,6-Dimethylbenzyloxy)phenyl)-4-oxobutyramide.

46. The biologically active agent of claim 32, wherein the agent is a compound of the formula:



wherein

n is 1 or 2;

m is 0;

R<sup>1</sup> is H or alkyl having from 1 to 7 carbon atoms;

or when R<sup>1</sup> is hydrogen, a pharmaceutically acceptable salt of the compound.

47. The agent of claim 46, wherein the compound is 4-(4-(2,6-difluorobenzyloxy)phenyl)-4-oxobutyric acid.

48. The agent of claim 46, wherein the compound is Ethyl 4-(4-(2,6-difluorobenzyloxy)phenyl)-4-oxobutyrate.

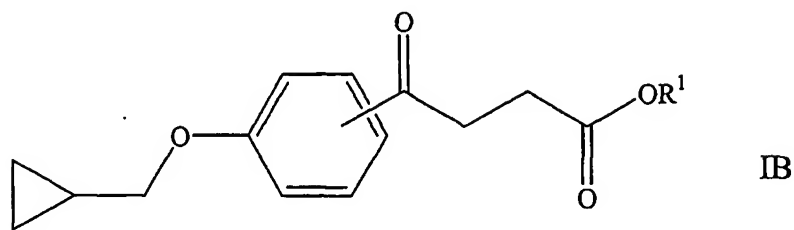
49. The agent of claim 46, wherein the compound is 4-(3-(2,6-difluorobenzyloxy)phenyl)-4-oxobutyric acid.

50. The agent of claim 46, wherein the compound is 4-(2-(2,6-difluorobenzyloxy)phenyl)-4-oxobutyric acid.



51. The agent of claim 21, wherein one of  $R^2$  and  $R^3$  is methyl, methoxy or perfluoromethyl and the other is hydrogen or methyl.
52. The agent of claim 51, wherein  $R^2$  is methyl, methoxy or perfluoromethyl and  $R^3$  is hydrogen.
53. The agent of claim 52, wherein the compound is 4-(4-(2-methoxybenzyloxy)phenyl)-4-oxobutyric acid.
54. The agent of claim 52, wherein the compound is 4-(4-(2-methylbenzyloxy)phenyl)-4-oxobutyric acid.
55. The agent of claim 52, wherein the compound is 4-(3-(2-methylbenzyloxy)phenyl)-4-oxobutyric acid.
56. The agent of claim 52, wherein the compound is Ethyl 4-(4-(2-methylbenzyloxy)phenyl)-4-oxobutyrate.
57. The agent of claim 52, wherein the compound is 4-(4-(2-trifluoromethylbenzyloxy)phenyl)-4-oxobutyric acid.
58. The agent of claim 51, wherein  $R^2$  is methyl and  $R^3$  is methyl.
59. The agent of claim 58, wherein the compound is 4-(4-(2,5-dimethylbenzyloxy)phenyl)-4-oxobutyric acid.
60. The agent of claim 58, wherein the compound is 4-(3-(2,6-dimethylbenzyloxy)phenyl)-4-oxobutyric acid.
61. The agent of claim 21, wherein  $R^2$  is hydrogen and  $R^3$  is hydrogen.
62. The agent of claim 61, wherein the compound is 4-(4-(benzyloxy)phenyl)-4-oxobutyric acid.

63. The biologically active agent of claim 2, wherein the agent is a compound of the formula:



wherein

$R^1$  is hydrogen or alkyl having from 1 to 7 carbon atoms,

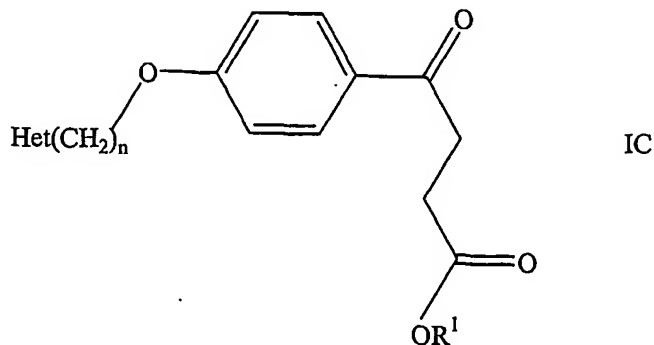
or when  $R^1$  is hydrogen, a pharmaceutically acceptable salt of the compound.

64. The agent of claim 63, wherein  $R^1$  is hydrogen or ethyl.

65. The agent of claim 64, wherein the compound is 4-(4-((cyclopropyl)methoxy)phenyl)-4-oxobutyric acid.

66. The agent of claim 64, wherein the compound is 4-(3-((cyclopropyl)methoxy)phenyl)-4-oxobutyric acid.

67. The biologically active agent of claim 2, wherein the agent is a compound of the formula:



wherein

n is 1 or 2;

R<sup>1</sup> is hydrogen or alkyl having from 1 to 7 carbon atoms; and

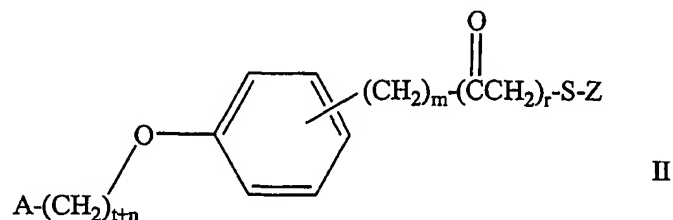
Het is a 5 or 6 membered heteroaromatic ring having 1 or 2 ring heteroatoms selected from N, S and O and the heteroaromatic ring is covalently bound to the remainder of the compound of formula IC by a ring carbon.

68. The agent of claim 67, wherein R<sup>1</sup> is hydrogen or ethyl.

69. The agent of claim 68, wherein the compound is 4-(4-((2-pyridinyl)-methoxy)phenyl)-4-oxobutyric acid.

70. The agent of claim 68, wherein the compound is 4-(4-(2-(2-thienyl)ethoxy)phenyl)-4-oxobutyric acid.

71. A biologically active agent, wherein the agent is a compound of the formula:



wherein

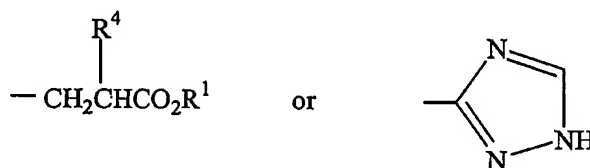
n is 1 or 2;

t is 0 or 1;

m is 0 and r is 1, or m is 1 and r is 0;

A is phenyl, unsubstituted or substituted by 1 or 2 groups selected from: halo, alkyl having 1 or 2 carbon atoms, perfluoromethyl, alkoxy having 1 or 2 carbon atoms, and perfluoromethoxy; or cycloalkyl having from 3 to 6 ring carbon atoms wherein the cycloalkyl is unsubstituted or one or two ring carbons are mono-substituted by methyl or ethyl; or a 5 or 6 membered heteroaromatic ring having 1 or 2 ring heteroatoms selected from N, S and O and the heteroaromatic ring is covalently bound to the remainder of the compound of formula II by a ring carbon;

Z is



R<sup>1</sup> is hydrogen or alkyl having from 1 to 7 carbon atoms;

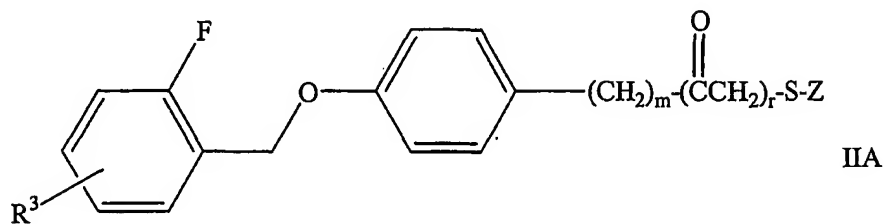
R<sup>4</sup> is hydrogen; -NHCOOC(CH<sub>3</sub>)<sub>3</sub>; -NHCH<sub>3</sub>; or -NHCH<sub>2</sub>CH<sub>3</sub>;

or when R<sup>1</sup> is hydrogen, a pharmaceutically acceptable salt of the compound.

72. The agent of claim 71, wherein A is cycloalkyl having from 3 to 6 ring carbon atoms wherein the cycloalkyl is unsubstituted or one or both of the ring carbons adjacent to the remainder of the compound of formula II are mono-substituted by methyl or ethyl.

73. The agent of claim 71, wherein A is phenyl, unsubstituted or substituted by 1 or 2 groups selected from: fluoro, alkyl having 1 or 2 carbon atoms, perfluoromethyl, alkoxy having 1 or 2 carbon atoms, and perfluoromethoxy.

74. The biologically active agent of claim 73, wherein the agent is a compound of the formula:

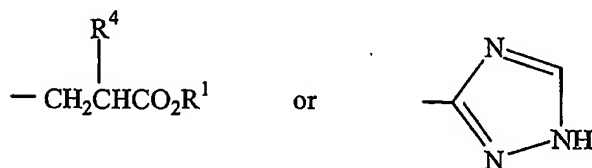


wherein

m is 0 or 1;

r is 0 or 1;

Z is



R¹ is hydrogen or alkyl having from 1 to 7 carbon atoms;

R⁴ is hydrogen; -NHCOOC(CH₃)₃; -NHCH₃; or -NHCH₂CH₃;

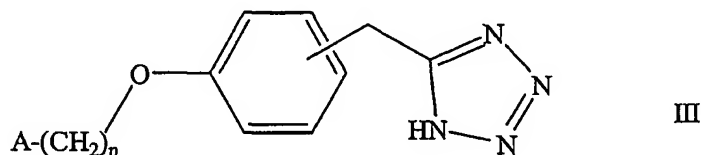
R³ is hydrogen or halo;

or when R¹ is hydrogen, a pharmaceutically acceptable salt of the compound.

75. The agent of claim 74, wherein R¹ is hydrogen or ethyl.

76. The agent of claim 75, wherein the compound is 3-[(4-(2-fluorobenzyloxy)phenyl)-methylthio]propionic acid.

77. The agent of claim 75, wherein the compound is 3-[(4-(2,6-difluorobenzyloxy)phenyl)-methylthio]propionic acid.
78. The agent of claim 75, wherein the compound is 3-(2-(4-(2,6-difluorobenzyloxy)phenyl)-2-oxoethyl)thio-(1H-1,2,4)-triazole.
79. The agent of claim 75, wherein the compound is (2RS) 2-(N-Boc)-3-[2-(4-(2,6-difluorobenzyloxy)phenyl)-2-oxoethyl]thiopropionic acid.
80. A biologically active agent, wherein the agent is a compound of the formula:



wherein

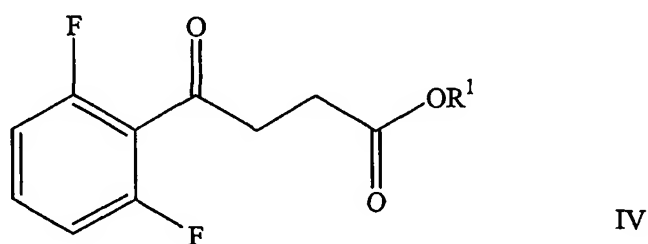
$n$  is 1 or 2;

A is phenyl, unsubstituted or substituted by 1 or 2 groups selected from: halo, alkyl having 1 or 2 carbon atoms, perfluoromethyl, alkoxy having 1 or 2 carbon atoms, and perfluoromethoxy; or cycloalkyl having from 3 to 6 ring carbon atoms wherein one or both ring carbons are independently mono-substituted by methyl or ethyl; or a 5 or 6 membered heteroaromatic ring having 1 or 2 ring heteroatoms selected from N, S and O and the heteroaromatic ring is covalently bound to the remainder of the compound of formula III by a ring carbon.

81. The agent of claim 80, wherein A is phenyl, unsubstituted or substituted by 1 or 2 groups selected from: halo, alkyl having 1 or 2 carbon atoms, perfluoromethyl, alkoxy having 1 or 2 carbon atoms, and perfluoromethoxy.

82. The agent of claim 81, wherein the compound is 5-[(4-(2,6-difluorobenzyloxy)phenyl)-methyl]-1H-tetrazole.

83. A biologically active agent, wherein the agent is a compound of the formula:



wherein

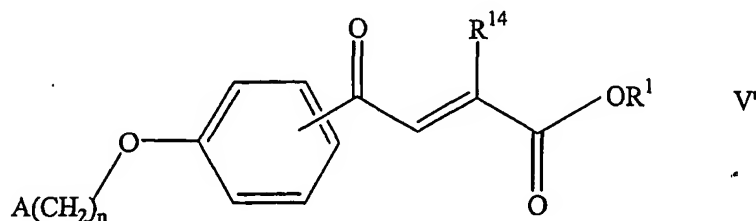
$R^1$  is hydrogen or alkyl having from 1 to 7 carbon atoms;

or when  $R^1$  is hydrogen, a pharmaceutically acceptable salt of the compound.

84. The agent of claim 83, wherein  $R^1$  is hydrogen or ethyl.

85. The agent of claim 84, wherein the compound is 4-(2,6-difluorophenyl)-4-oxobutyric acid.

86. A biologically active agent, wherein the agent is a compound of the formula:



wherein

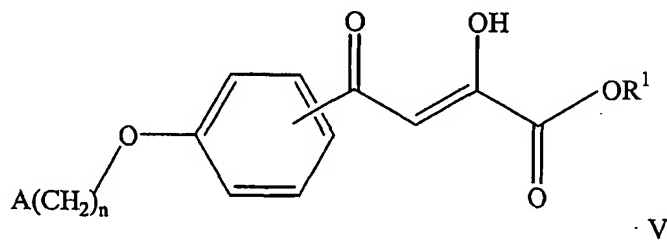
n is 1 or 2;

R<sup>1</sup> is hydrogen or alkyl having from 1 to 7 carbon atoms;

R<sup>14</sup> is hydroxy or hydrogen; and

A is phenyl, unsubstituted or substituted by 1 or 2 groups selected from halo, alkyl having 1 or 2 carbon atoms, perfluoromethyl, alkoxy having 1 or 2 carbon atoms, and perfluoromethoxy; or cycloalkyl having from 3 to 6 ring carbon atoms wherein the cycloalkyl is unsubstituted or one or two ring carbons are independently mono-substituted by methyl or ethyl; or a 5 or 6 membered heteroaromatic ring having 1 or 2 ring heteroatoms selected from N, S and O and the heteroaromatic ring is covalently bound to the remainder of the compound of formula I by a ring carbon; or a pharmaceutically acceptable salt of the compound.

87. The biologically active agent of claim 86, wherein the agent is a compound of the formula:



wherein

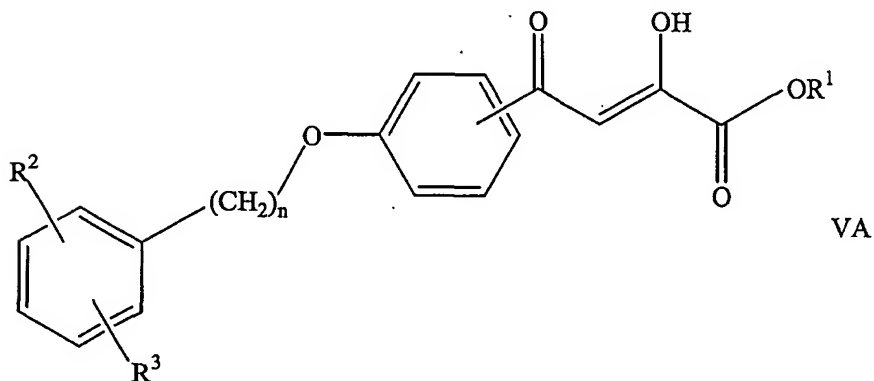
n is 1 or 2;

R<sup>1</sup> is hydrogen or alkyl having from 1 to 7 carbon atoms;



A is phenyl, unsubstituted or substituted by 1 or 2 groups selected from halo, alkyl having 1 or 2 carbon atoms, perfluoromethyl, alkoxy having 1 or 2 carbon atoms, and perfluoromethoxy; or cycloalkyl having from 3 to 6 ring carbon atoms wherein the cycloalkyl is unsubstituted or one or two ring carbons are independently mono-substituted by methyl or ethyl; or a 5 or 6 membered heteroaromatic ring having 1 or 2 ring heteroatoms selected from N, S and O and the heteroaromatic ring is covalently bound to the remainder of the compound of formula I by a ring carbon; or a pharmaceutically acceptable salt of the compound.

88. The biologically active agent of claim 87, wherein the agent is a compound of the formula:



wherein

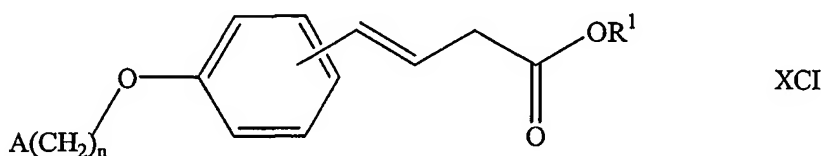
n is 1 or 2;

R¹ is hydrogen or alkyl having from 1 to 7 carbon atoms;

R² and R³ are each independently selected from hydrogen, halo, alkyl having 1 or 2 carbon atoms, perfluoromethyl, alkoxy having 1 or 2 carbon atoms, and perfluoromethoxy;

or a pharmaceutically acceptable salt of the compound.

89. The agent of claim 88, wherein  $R^1$  is hydrogen or ethyl.
90. The agent of claim 89, wherein the compound is ethyl 2-hydroxy-4-oxo-4-(4-(2,6-difluorobenzyloxy)phenyl) but-2-enoate.
91. The agent of claim 86, wherein the compound is 4-(3-(2,6-Dimethylbenzyloxy)phenyl)-4-oxo-2-butenic acid.
92. A biologically active agent, wherein the agent is a compound of the formula:



wherein

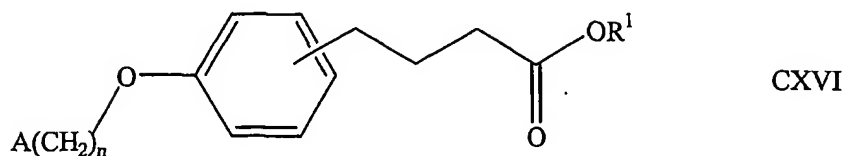
$n$  is 1 or 2;

$R^1$  is hydrogen or alkyl having from 1 to 3 carbon atoms; and

A is phenyl, unsubstituted or substituted by 1 or 2 groups selected from halo, alkyl having 1 or 2 carbon atoms, perfluoromethyl, alkoxy having 1 or 2 carbon atoms, and perfluoromethoxy; or cycloalkyl having from 3 to 6 ring carbon atoms wherein the cycloalkyl is unsubstituted or one or two ring carbons are independently mono-substituted by methyl or ethyl; or a 5 or 6 membered heteroaromatic ring having 1 or 2 ring heteroatoms selected from N, S and O and the heteroaromatic ring is covalently bound to the remainder of the compound of formula I by a ring carbon; or a pharmaceutically acceptable salt of the compound.

93. The agent of claim 92, wherein the compound is 4-(3-(2,6-Dimethylbenzyloxy)phenyl)-3-butenic acid.

94. A biologically active agent, wherein the agent is a compound of the formula:



wherein

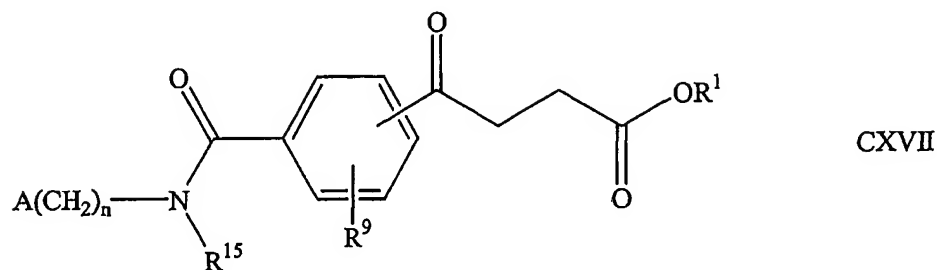
n is 1 or 2;

R<sup>1</sup> is hydrogen or alkyl having from 1 to 3 carbon atoms; and

A is phenyl, unsubstituted or substituted by 1 or 2 groups selected from halo, alkyl having 1 or 2 carbon atoms, perfluoromethyl, alkoxy having 1 or 2 carbon atoms, and perfluoromethoxy; or cycloalkyl having from 3 to 6 ring carbon atoms wherein the cycloalkyl is unsubstituted or one or two ring carbons are independently mono-substituted by methyl or ethyl; or a 5 or 6 membered heteroaromatic ring having 1 or 2 ring heteroatoms selected from N, S and O and the heteroaromatic ring is covalently bound to the remainder of the compound of formula I by a ring carbon; or a pharmaceutically acceptable salt of the compound.

95. The agent of claim 94, wherein the compound is 4-(3-(2,6-Dimethylbenzyloxy)phenyl)butyric acid.

96. A biologically active agent, wherein the agent is a compound of the formula:



wherein

n is 0, 1 or 2;

R<sup>1</sup> is hydrogen or alkyl having from 1 to 3 carbon atoms;

R<sup>15</sup> is hydrogen or alkyl having from 1 to 3 carbon atoms;

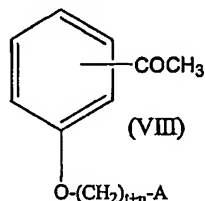
R<sup>9</sup> is hydrogen, halo, hydroxy, or alkoxy having from 1 to 3 carbon atoms;

A is phenyl, unsubstituted or substituted by 1 or 2 groups selected from halo, alkyl having 1 or 2 carbon atoms, perfluoromethyl, alkoxy having 1 or 2 carbon atoms, and perfluoromethoxy; or cycloalkyl having from 3 to 6 ring carbon atoms wherein the cycloalkyl is unsubstituted or one or two ring carbons are independently mono-substituted by methyl or ethyl; or a 5 or 6 membered heteroaromatic ring having 1 or 2 ring heteroatoms selected from N, S and O and the heteroaromatic ring is covalently bound to the remainder of the compound of formula I by a ring carbon; or a pharmaceutically acceptable salt of the compound.

97. The agent of claim 96, wherein the compound is 4-[5-[[N-(4-Trifluoromethylbenzyl)aminocarbonyl]-2-methoxy]phenyl]-4-oxobutyric acid.

98. The agent of claim 96, wherein the compound is 4-[5-[[N-(2,6-Dimethylbenzyl)aminocarbonyl]-2-methoxy]phenyl]-4-oxobutyric acid.

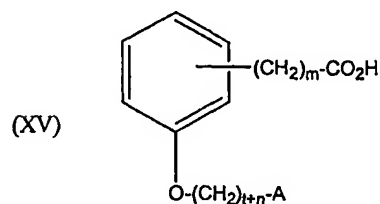
99. A compound of the formula:



wherein n is 1 or 2; t is 0 or 1; and

A is phenyl, unsubstituted or substituted by 1 or 2 groups selected from: halo, alkyl having 1 or 2 carbon atoms, perfluoromethyl, alkoxy having 1 or 2 carbon atoms, and perfluoromethoxy; or cycloalkyl having from 3 to 6 ring carbon atoms wherein the cycloalkyl is unsubstituted or one or two ring carbons are independently mono-substituted by methyl or ethyl; or a 5 or 6 membered heteroaromatic ring having 1 or 2 ring heteroatoms selected from N, S and O and the heteroaromatic ring is covalently bound to the remainder of the compound by a ring carbon.

100. A compound of the formula:

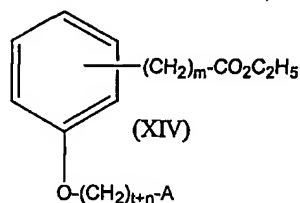


wherein m is 1; n is 1 or 2; t is 0 or 1; and

A is phenyl, unsubstituted or substituted by 1 or 2 groups selected from: halo, alkyl having 1 or 2 carbon atoms, perfluoromethyl, alkoxy having 1 or 2 carbon atoms, and perfluoromethoxy; or cycloalkyl having from 3 to 6 ring carbon atoms wherein the cycloalkyl is unsubstituted or one or two ring carbons are independently mono-substituted by methyl or ethyl; or

a 5 or 6 membered heteroaromatic ring having 1 or 2 ring heteroatoms selected from N, S and O and the heteroaromatic ring is covalently bound to the remainder of the compound by a ring carbon.

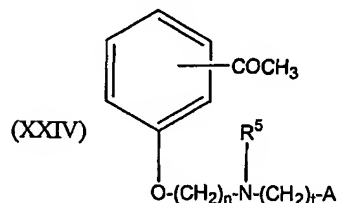
101. A compound of the formula:



wherein m is 1; n is 1 or 2; t is 0 or 1; and

A is phenyl, unsubstituted or substituted by 1 or 2 groups selected from: halo, alkyl having 1 or 2 carbon atoms, perfluoromethyl, alkoxy having 1 or 2 carbon atoms, and perfluoromethoxy; or cycloalkyl having from 3 to 6 ring carbon atoms wherein the cycloalkyl is unsubstituted or one or two ring carbons are independently mono-substituted by methyl or ethyl; or a 5 or 6 membered heteroaromatic ring having 1 or 2 ring heteroatoms selected from N, S and O and the heteroaromatic ring is covalently bound to the remainder of the compound by a ring carbon.

102. A compound of the formula:

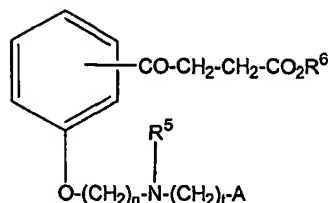


wherein R<sup>5</sup> is alkyl having from 1 to 3 carbon atoms; n is 1 or 2; t is 0 or 1; and

A is phenyl, unsubstituted or substituted by 1 or 2 groups selected from: halo, alkyl having 1 or 2 carbon atoms, perfluoromethyl, alkoxy having 1 or 2 carbon atoms, and perfluoromethoxy; or

cycloalkyl having from 3 to 6 ring carbon atoms wherein the cycloalkyl is unsubstituted or one or two ring carbons are independently mono-substituted by methyl or ethyl; or  
 a 5 or 6 membered heteroaromatic ring having 1 or 2 ring heteroatoms selected from N, S and O and the heteroaromatic ring is covalently bound to the remainder of the compound by a ring carbon.

103. A compound of the formula:

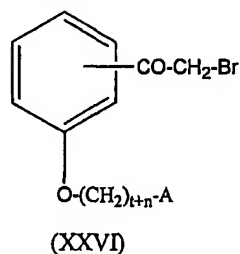


(XXV)

wherein  $\text{R}^5$  is alkyl having from 1 to 3 carbon atoms;  $\text{R}^6$  is alkyl having from 1 to 7 carbon atoms; n is 1 or 2; t is 0 or 1; and

A is phenyl, unsubstituted or substituted by 1 or 2 groups selected from: halo, alkyl having 1 or 2 carbon atoms, perfluoromethyl, alkoxy having 1 or 2 carbon atoms, and perfluoromethoxy; or  
 cycloalkyl having from 3 to 6 ring carbon atoms wherein the cycloalkyl is unsubstituted or one or two ring carbons are independently mono-substituted by methyl or ethyl; or  
 a 5 or 6 membered heteroaromatic ring having 1 or 2 ring heteroatoms selected from N, S and O and the heteroaromatic ring is covalently bound to the remainder of the compound by a ring carbon.

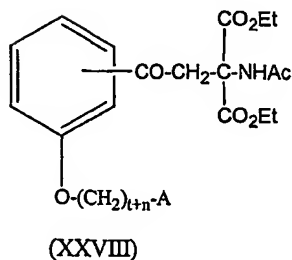
104. A compound of the formula:



wherein n is 1 or 2; t is 0 or 1; and

- A is phenyl, unsubstituted or substituted by 1 or 2 groups selected from:  
 halo, alkyl having 1 or 2 carbon atoms, perfluoromethyl, alkoxy having 1 or 2 carbon atoms, and perfluoromethoxy; or  
 cycloalkyl having from 3 to 6 ring carbon atoms wherein the cycloalkyl is unsubstituted or one or two ring carbons are independently mono-substituted by methyl or ethyl; or  
 a 5 or 6 membered heteroaromatic ring having 1 or 2 ring heteroatoms selected from N, S and O and the heteroaromatic ring is covalently bound to the remainder of the compound by a ring carbon.

105. A compound of the formula:



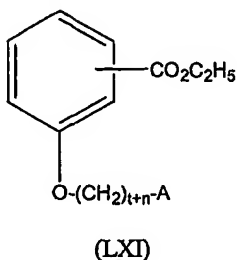
wherein n is 1 or 2; t is 0 or 1; and

- A is phenyl, unsubstituted or substituted by 1 or 2 groups selected from:  
 halo, alkyl having 1 or 2 carbon atoms, perfluoromethyl, alkoxy having 1 or 2 carbon atoms, and perfluoromethoxy; or  
 cycloalkyl having from 3 to 6 ring carbon atoms wherein the cycloalkyl is unsubstituted or one or two ring carbons are independently mono-substituted by methyl or ethyl; or



a 5 or 6 membered heteroaromatic ring having 1 or 2 ring heteroatoms selected from N, S and O and the heteroaromatic ring is covalently bound to the remainder of the compound by a ring carbon.

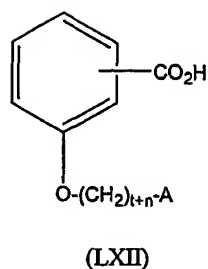
106. A compound of the formula:



wherein n is 1 or 2; t is 0 or 1; and

A is phenyl, unsubstituted or substituted by 1 or 2 groups selected from: halo, alkyl having 1 or 2 carbon atoms, perfluoromethyl, alkoxy having 1 or 2 carbon atoms, and perfluoromethoxy; or cycloalkyl having from 3 to 6 ring carbon atoms wherein the cycloalkyl is unsubstituted or one or two ring carbons are independently mono-substituted by methyl or ethyl; or a 5 or 6 membered heteroaromatic ring having 1 or 2 ring heteroatoms selected from N, S and O and the heteroaromatic ring is covalently bound to the remainder of the compound by a ring carbon.

107. A compound of the formula:

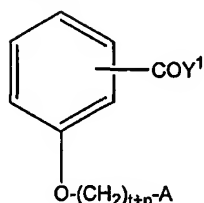


wherein n is 1 or 2; t is 0 or 1; and

A is phenyl, unsubstituted or substituted by 1 or 2 groups selected from: halo, alkyl having 1 or 2 carbon atoms, perfluoromethyl, alkoxy having 1 or 2 carbon atoms, and perfluoromethoxy; or

cycloalkyl having from 3 to 6 ring carbon atoms wherein the cycloalkyl is unsubstituted or one or two ring carbons are independently mono-substituted by methyl or ethyl; or  
 a 5 or 6 membered heteroaromatic ring having 1 or 2 ring heteroatoms selected from N, S and O and the heteroaromatic ring is covalently bound to the remainder of the compound by a ring carbon.

108. A compound of the formula:

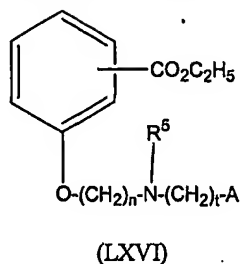


(LXIII)

wherein Y¹ is chloro; n is 1 or 2; t is 0 or 1; and

A is phenyl, unsubstituted or substituted by 1 or 2 groups selected from:  
 halo, alkyl having 1 or 2 carbon atoms, perfluoromethyl, alkoxy having 1 or 2 carbon atoms, and perfluoromethoxy; or  
 cycloalkyl having from 3 to 6 ring carbon atoms wherein the cycloalkyl is unsubstituted or one or two ring carbons are independently mono-substituted by methyl or ethyl; or  
 a 5 or 6 membered heteroaromatic ring having 1 or 2 ring heteroatoms selected from N, S and O and the heteroaromatic ring is covalently bound to the remainder of the compound by a ring carbon.

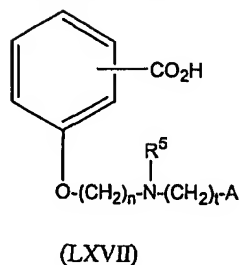
109. A compound of the formula:



wherein  $R^5$  is alkyl having from 1 to 3 carbon atoms; n is 1 or 2; t is 0 or 1; and

A is phenyl, unsubstituted or substituted by 1 or 2 groups selected from:  
halo, alkyl having 1 or 2 carbon atoms, perfluoromethyl, alkoxy having 1 or 2 carbon atoms, and perfluoromethoxy; or  
cycloalkyl having from 3 to 6 ring carbon atoms wherein the cycloalkyl is unsubstituted or one or two ring carbons are independently mono-substituted by methyl or ethyl; or  
a 5 or 6 membered heteroaromatic ring having 1 or 2 ring heteroatoms selected from N, S and O and the heteroaromatic ring is covalently bound to the remainder of the compound by a ring carbon.

110. A compound of the formula:

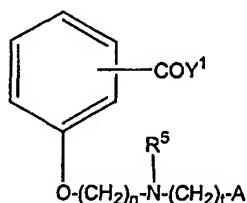


wherein  $R^5$  is alkyl having from 1 to 3 carbon atoms; n is 1 or 2; t is 0 or 1; and

A is phenyl, unsubstituted or substituted by 1 or 2 groups selected from:  
halo, alkyl having 1 or 2 carbon atoms, perfluoromethyl, alkoxy having 1 or 2 carbon atoms, and perfluoromethoxy; or  
cycloalkyl having from 3 to 6 ring carbon atoms wherein the cycloalkyl is unsubstituted or one or two ring carbons are independently mono-substituted by methyl or ethyl; or

a 5 or 6 membered heteroaromatic ring having 1 or 2 ring heteroatoms selected from N, S and O and the heteroaromatic ring is covalently bound to the remainder of the compound by a ring carbon.

111. A compound of the formula:

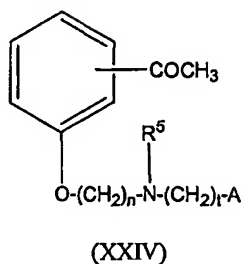


(LXVIII)

wherein  $\text{R}^5$  is alkyl having from 1 to 3 carbon atoms;  $\text{Y}^1$  is chloro;  $n$  is 1 or 2;  $t$  is 0 or 1; and

- A is phenyl, unsubstituted or substituted by 1 or 2 groups selected from: halo, alkyl having 1 or 2 carbon atoms, perfluoromethyl, alkoxy having 1 or 2 carbon atoms, and perfluoromethoxy; or cycloalkyl having from 3 to 6 ring carbon atoms wherein the cycloalkyl is unsubstituted or one or two ring carbons are independently mono-substituted by methyl or ethyl; or a 5 or 6 membered heteroaromatic ring having 1 or 2 ring heteroatoms selected from N, S and O and the heteroaromatic ring is covalently bound to the remainder of the compound by a ring carbon.

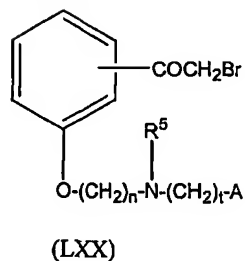
112. A compound of the formula:



wherein  $R^5$  is alkyl having from 1 to 3 carbon atoms; n is 1 or 2; t is 0 or 1; and

A is phenyl, unsubstituted or substituted by 1 or 2 groups selected from: halo, alkyl having 1 or 2 carbon atoms, perfluoromethyl, alkoxy having 1 or 2 carbon atoms, and perfluoromethoxy; or cycloalkyl having from 3 to 6 ring carbon atoms wherein the cycloalkyl is unsubstituted or one or two ring carbons are independently mono-substituted by methyl or ethyl; or a 5 or 6 membered heteroaromatic ring having 1 or 2 ring heteroatoms selected from N, S and O and the heteroaromatic ring is covalently bound to the remainder of the compound by a ring carbon.

113. A compound of the formula:

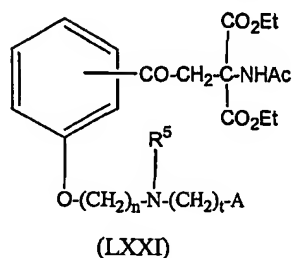


wherein  $R^5$  is alkyl having from 1 to 3 carbon atoms; n is 1 or 2; t is 0 or 1; and

A is phenyl, unsubstituted or substituted by 1 or 2 groups selected from: halo, alkyl having 1 or 2 carbon atoms, perfluoromethyl, alkoxy having 1 or 2 carbon atoms, and perfluoromethoxy; or cycloalkyl having from 3 to 6 ring carbon atoms wherein the cycloalkyl is unsubstituted or one or two ring carbons are independently mono-substituted by methyl or ethyl; or

a 5 or 6 membered heteroaromatic ring having 1 or 2 ring heteroatoms selected from N, S and O and the heteroaromatic ring is covalently bound to the remainder of the compound by a ring carbon.

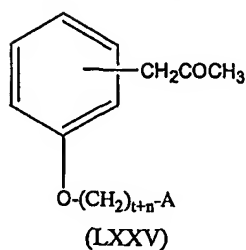
114. A compound of the formula:



wherein  $R^5$  is alkyl having from 1 to 3 carbon atoms;  $n$  is 1 or 2;  $t$  is 0 or 1; and

A is phenyl, unsubstituted or substituted by 1 or 2 groups selected from: halo, alkyl having 1 or 2 carbon atoms, perfluoromethyl, alkoxy having 1 or 2 carbon atoms, and perfluoromethoxy; or cycloalkyl having from 3 to 6 ring carbon atoms wherein the cycloalkyl is unsubstituted or one or two ring carbons are independently mono-substituted by methyl or ethyl; or a 5 or 6 membered heteroaromatic ring having 1 or 2 ring heteroatoms selected from N, S and O and the heteroaromatic ring is covalently bound to the remainder of the compound by a ring carbon.

115. A compound of the formula:

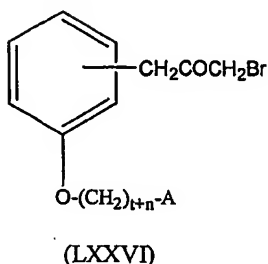


wherein  $n$  is 1 or 2;  $t$  is 0 or 1; and

A is phenyl, unsubstituted or substituted by 1 or 2 groups selected from: halo, alkyl having 1 or 2 carbon atoms, perfluoromethyl, alkoxy having 1 or 2 carbon atoms, and perfluoromethoxy; or

cycloalkyl having from 3 to 6 ring carbon atoms wherein the cycloalkyl is unsubstituted or one or two ring carbons are independently mono-substituted by methyl or ethyl; or  
 a 5 or 6 membered heteroaromatic ring having 1 or 2 ring heteroatoms selected from N, S and O and the heteroaromatic ring is covalently bound to the remainder of the compound by a ring carbon.

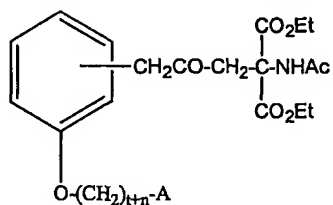
116. A compound of the formula:



wherein n is 1 or 2; t is 0 or 1; and

A is phenyl, unsubstituted or substituted by 1 or 2 groups selected from:  
 halo, alkyl having 1 or 2 carbon atoms, perfluoromethyl, alkoxy having 1 or 2 carbon atoms, and perfluoromethoxy; or  
 cycloalkyl having from 3 to 6 ring carbon atoms wherein the cycloalkyl is unsubstituted or one or two ring carbons are independently mono-substituted by methyl or ethyl; or  
 a 5 or 6 membered heteroaromatic ring having 1 or 2 ring heteroatoms selected from N, S and O and the heteroaromatic ring is covalently bound to the remainder of the compound by a ring carbon.

117. A compound of the formula:

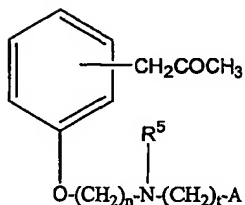


(LXXVII)

wherein n is 1 or 2; t is 0 or 1; and

A is phenyl, unsubstituted or substituted by 1 or 2 groups selected from: halo, alkyl having 1 or 2 carbon atoms, perfluoromethyl, alkoxy having 1 or 2 carbon atoms, and perfluoromethoxy; or cycloalkyl having from 3 to 6 ring carbon atoms wherein the cycloalkyl is unsubstituted or one or two ring carbons are independently mono-substituted by methyl or ethyl; or a 5 or 6 membered heteroaromatic ring having 1 or 2 ring heteroatoms selected from N, S and O and the heteroaromatic ring is covalently bound to the remainder of the compound by a ring carbon.

118. A compound of the formula:



(LXXX)

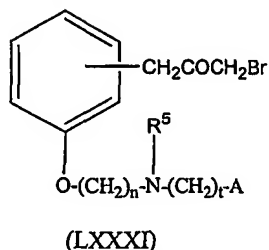
wherein R<sup>5</sup> is alkyl having from 1 to 3 carbon atoms; n is 1 or 2; t is 0 or 1; and

A is phenyl, unsubstituted or substituted by 1 or 2 groups selected from: halo, alkyl having 1 or 2 carbon atoms, perfluoromethyl, alkoxy having 1 or 2 carbon atoms, and perfluoromethoxy; or cycloalkyl having from 3 to 6 ring carbon atoms wherein the cycloalkyl is unsubstituted or one or two ring carbons are independently mono-substituted by methyl or ethyl; or



a 5 or 6 membered heteroaromatic ring having 1 or 2 ring heteroatoms selected from N, S and O and the heteroaromatic ring is covalently bound to the remainder of the compound by a ring carbon.

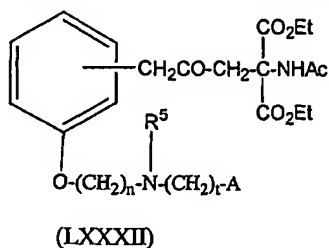
119. A compound of the formula:



wherein  $R^5$  is alkyl having from 1 to 3 carbon atoms;  $n$  is 1 or 2;  $t$  is 0 or 1; and

A is phenyl, unsubstituted or substituted by 1 or 2 groups selected from: halo, alkyl having 1 or 2 carbon atoms, perfluoromethyl, alkoxy having 1 or 2 carbon atoms, and perfluoromethoxy; or cycloalkyl having from 3 to 6 ring carbon atoms wherein the cycloalkyl is unsubstituted or one or two ring carbons are independently mono-substituted by methyl or ethyl; or a 5 or 6 membered heteroaromatic ring having 1 or 2 ring heteroatoms selected from N, S and O and the heteroaromatic ring is covalently bound to the remainder of the compound by a ring carbon.

120. A compound of the formula:

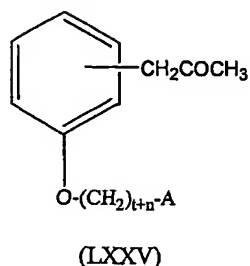


wherein  $R^5$  is alkyl having from 1 to 3 carbon atoms;  $n$  is 1 or 2;  $t$  is 0 or 1; and

A is phenyl, unsubstituted or substituted by 1 or 2 groups selected from: halo, alkyl having 1 or 2 carbon atoms, perfluoromethyl, alkoxy having 1 or 2 carbon atoms, and perfluoromethoxy; or

cycloalkyl having from 3 to 6 ring carbon atoms wherein the cycloalkyl is unsubstituted or one or two ring carbons are independently mono-substituted by methyl or ethyl; or  
 a 5 or 6 membered heteroaromatic ring having 1 or 2 ring heteroatoms selected from N, S and O and the heteroaromatic ring is covalently bound to the remainder of the compound by a ring carbon.

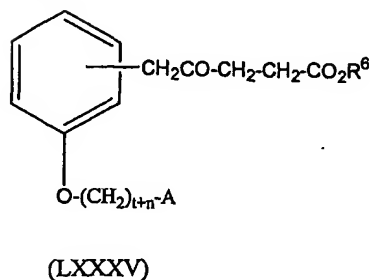
121. A compound of the formula:



wherein n is 1 or 2; t is 0 or 1; and

A is phenyl, unsubstituted or substituted by 1 or 2 groups selected from:  
 halo, alkyl having 1 or 2 carbon atoms, perfluoromethyl, alkoxy having 1 or 2 carbon atoms, and perfluoromethoxy; or  
 cycloalkyl having from 3 to 6 ring carbon atoms wherein the cycloalkyl is unsubstituted or one or two ring carbons are independently mono-substituted by methyl or ethyl; or  
 a 5 or 6 membered heteroaromatic ring having 1 or 2 ring heteroatoms selected from N, S and O and the heteroaromatic ring is covalently bound to the remainder of the compound by a ring carbon.

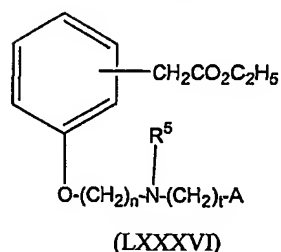
122. A compound of the formula:



wherein  $R^6$  is alkyl having from 1 to 7 carbon atoms; n is 1 or 2; t is 0 or 1; and

- A is phenyl, unsubstituted or substituted by 1 or 2 groups selected from:  
 halo, alkyl having 1 or 2 carbon atoms, perfluoromethyl, alkoxy having 1 or 2 carbon atoms, and perfluoromethoxy; or  
 cycloalkyl having from 3 to 6 ring carbon atoms wherein the cycloalkyl is unsubstituted or one or two ring carbons are independently mono-substituted by methyl or ethyl; or  
 a 5 or 6 membered heteroaromatic ring having 1 or 2 ring heteroatoms selected from N, S and O and the heteroaromatic ring is covalently bound to the remainder of the compound by a ring carbon.

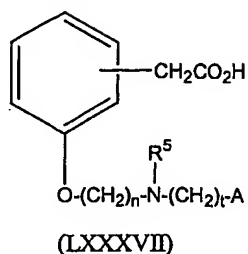
123. A compound of the formula:



wherein  $R^5$  is alkyl having from 1 to 3 carbon atoms; n is 1 or 2; t is 0 or 1; and

- A is phenyl, unsubstituted or substituted by 1 or 2 groups selected from:  
 halo, alkyl having 1 or 2 carbon atoms, perfluoromethyl, alkoxy having 1 or 2 carbon atoms, and perfluoromethoxy; or  
 cycloalkyl having from 3 to 6 ring carbon atoms wherein the cycloalkyl is unsubstituted or one or two ring carbons are independently mono-substituted by methyl or ethyl; or  
 a 5 or 6 membered heteroaromatic ring having 1 or 2 ring heteroatoms selected from N, S and O and the heteroaromatic ring is covalently bound to the remainder of the compound by a ring carbon.

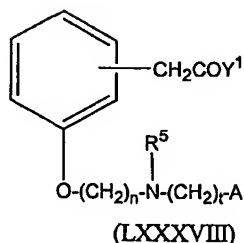
124. A compound of the formula:



wherein  $R^5$  is alkyl having from 1 to 3 carbon atoms;  $n$  is 1 or 2;  $t$  is 0 or 1; and

A is phenyl, unsubstituted or substituted by 1 or 2 groups selected from:  
halo, alkyl having 1 or 2 carbon atoms, perfluoromethyl, alkoxy having 1 or 2 carbon atoms, and perfluoromethoxy; or  
cycloalkyl having from 3 to 6 ring carbon atoms wherein the cycloalkyl is unsubstituted or one or two ring carbons are independently mono-substituted by methyl or ethyl; or  
a 5 or 6 membered heteroaromatic ring having 1 or 2 ring heteroatoms selected from N, S and O and the heteroaromatic ring is covalently bound to the remainder of the compound by a ring carbon.

125. A compound of the formula:

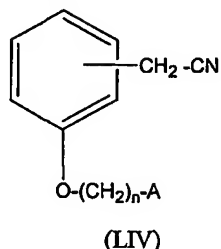


wherein  $R^5$  is alkyl having from 1 to 3 carbon atoms;  $Y^1$  is chloro;  $n$  is 1 or 2;  $t$  is 0 or 1; and

A is phenyl, unsubstituted or substituted by 1 or 2 groups selected from:  
halo, alkyl having 1 or 2 carbon atoms, perfluoromethyl, alkoxy having 1 or 2 carbon atoms, and perfluoromethoxy; or  
cycloalkyl having from 3 to 6 ring carbon atoms wherein the cycloalkyl is unsubstituted or one or two ring carbons are independently mono-substituted by methyl or ethyl; or

a 5 or 6 membered heteroaromatic ring having 1 or 2 ring heteroatoms selected from N, S and O and the heteroaromatic ring is covalently bound to the remainder of the compound by a ring carbon.

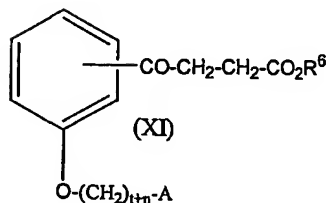
126. A compound of the formula:



wherein n is 1 or 2; and

A is phenyl, unsubstituted or substituted by 1 or 2 groups selected from: halo, alkyl having 1 or 2 carbon atoms, perfluoromethyl, alkoxy having 1 or 2 carbon atoms, and perfluoromethoxy; or cycloalkyl having from 3 to 6 ring carbon atoms wherein the cycloalkyl is unsubstituted or one or two ring carbons are independently mono-substituted by methyl or ethyl; or a 5 or 6 membered heteroaromatic ring having 1 or 2 ring heteroatoms selected from N, S and O and the heteroaromatic ring is covalently bound to the remainder of the compound by a ring carbon.

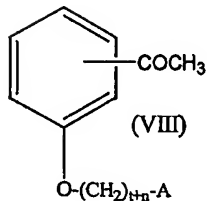
127. A process for producing a compound of the formula:



wherein  $R^6$  is alkyl having from 1 to 7 carbon atoms; n is 1 or 2; t is 0 or 1; and

A is phenyl, unsubstituted or substituted by 1 or 2 groups selected from: halo, alkyl having 1 or 2 carbon atoms, perfluoromethyl, alkoxy having 1 or 2 carbon atoms, and perfluoromethoxy; or

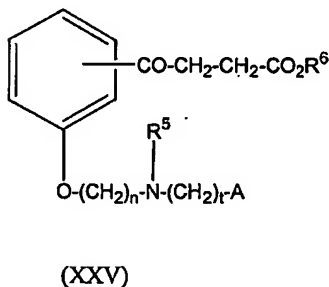
cycloalkyl having from 3 to 6 ring carbon atoms wherein the cycloalkyl is unsubstituted or one or two ring carbons are independently mono-substituted by methyl or ethyl; or  
 a 5 or 6 membered heteroaromatic ring having 1 or 2 ring heteroatoms selected from N, S and O and the heteroaromatic ring is covalently bound to the remainder of the compound by a ring carbon,  
 comprising, reacting a compound of the formula:



with a compound of the formula  $\text{BrCH}_2\text{CO}_2\text{R}^6$  in the presence of a base, wherein  $\text{R}^6$ , n, t and A are as above, to yield the corresponding compound of formula XI.

128. The process of claim 106, further comprising hydrolyzing the compound of formula XI to remove  $\text{R}^6$  and yield the corresponding acid.

129. A process for producing a compound of the formula:

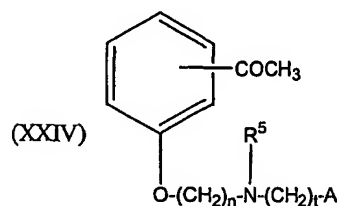


wherein  $\text{R}^5$  is alkyl having from 1 to 3 carbon atoms;  $\text{R}^6$  is alkyl having from 1 to 7 carbon atoms; n is 1 or 2; t is 0 or 1; and

A is phenyl, unsubstituted or substituted by 1 or 2 groups selected from:  
 halo, alkyl having 1 or 2 carbon atoms, perfluoromethyl, alkoxy having 1 or 2 carbon atoms, and perfluoromethoxy; or

cycloalkyl having from 3 to 6 ring carbon atoms wherein the cycloalkyl is unsubstituted or one or two ring carbons are independently mono-substituted by methyl or ethyl; or  
 a 5 or 6 membered heteroaromatic ring having 1 or 2 ring heteroatoms selected from N, S and O and the heteroaromatic ring is covalently bound to the remainder of the compound by a ring carbon,

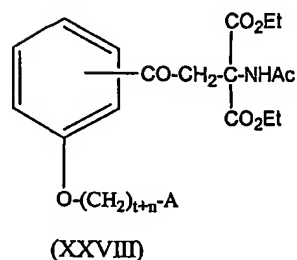
comprising, reacting a compound of the formula:



with a compound of the formula  $\text{BrCH}_2\text{CO}_2\text{R}^6$  in the presence of an alkali metal silyl amide, wherein  $\text{R}^6$ ,  $n$ ,  $t$  and  $\text{A}$  are as above, to yield the corresponding compound of formula XXV.

130. The process of claim 129, further comprising hydrolyzing the compound of formula XXV to remove  $\text{R}^6$  and yield the corresponding acid:

131. A process for producing a compound of the formula:



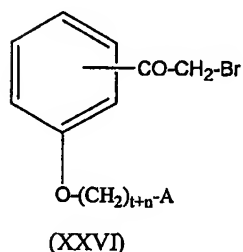
wherein  $n$  is 1 or 2;  $t$  is 0 or 1; and

$\text{A}$  is phenyl, unsubstituted or substituted by 1 or 2 groups selected from:  
 halo, alkyl having 1 or 2 carbon atoms, perfluoromethyl, alkoxy having 1 or 2 carbon atoms, and perfluoromethoxy; or

cycloalkyl having from 3 to 6 ring carbon atoms wherein the cycloalkyl is unsubstituted or one or two ring carbons are independently mono-substituted by methyl or ethyl; or

a 5 or 6 membered heteroaromatic ring having 1 or 2 ring heteroatoms selected from N, S and O and the heteroaromatic ring is covalently bound to the remainder of the compound by a ring carbon,

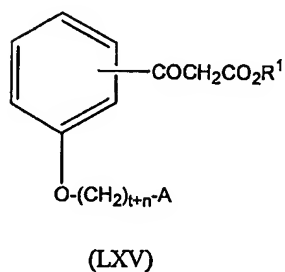
comprising, reacting a compound of the formula:



with the sodium salt of diethylacetamidomalonate, wherein n, t and A are as above,

to yield the corresponding compound of formula XXVIII.

132. A process for producing a compound of the formula:



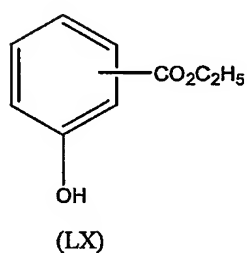
wherein R<sup>1</sup> is ethyl; n is 1 or 2; t is 0 or 1; and

A is phenyl, unsubstituted or substituted by 1 or 2 groups selected from: halo, alkyl having 1 or 2 carbon atoms, perfluoromethyl, alkoxy having 1 or 2 carbon atoms, and perfluoromethoxy; or

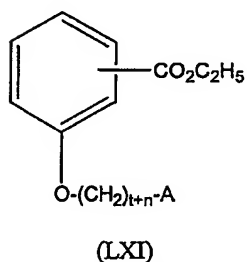


cycloalkyl having from 3 to 6 ring carbon atoms wherein the cycloalkyl is unsubstituted or one or two ring carbons are independently mono-substituted by methyl or ethyl; or  
 a 5 or 6 membered heteroaromatic ring having 1 or 2 ring heteroatoms selected from N, S and O and the heteroaromatic ring is covalently bound to the remainder of the compound by a ring carbon,  
 comprising,

a) reacting a compound of the formula:

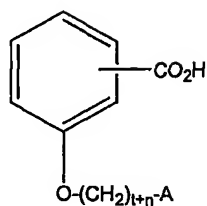


with either: i) a compound of formula  $A(CH_2)_{t+n}-OH$  under Mitsunobu conditions, or ii) a compound of formula  $A(CH_2)_{t+n}-Y$ , to yield the corresponding compound of the formula:



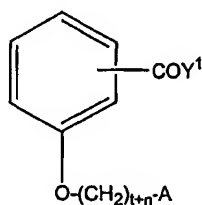
wherein n, t and A are as above and Y is a leaving group

b) hydrolyzing the compound of formula LXI to yield the corresponding compound of the formula:



(LXII)

- c) reacting the compound of formula LXII with thionyl chloride to yield the corresponding compound of the formula:

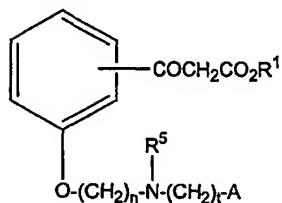


(LXIII)

wherein  $Y^1$  is chloro

- d) treating  $\text{EtOCOCH}_2\text{COOH}$  with about two equivalents of butyllithium;  
and  
e) reacting the compound of formula LXIII with the product resulting from steps d), to yield the compound of formula LXV.

133. A process for producing a compound of the formula:



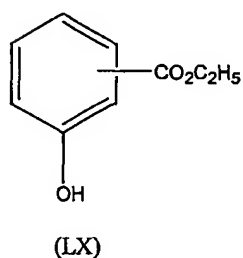
(LXIX)

wherein  $R^1$  is ethyl;  $R^5$  is alkyl having from 1 to 3 carbon atoms;  $n$  is 1 or 2;  $t$  is 0 or 1; and

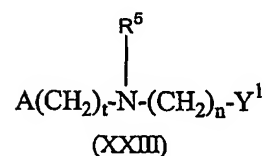
- A is phenyl, unsubstituted or substituted by 1 or 2 groups selected from:  
 halo, alkyl having 1 or 2 carbon atoms, perfluoromethyl, alkoxy having 1  
 or 2 carbon atoms, and perfluoromethoxy; or  
 cycloalkyl having from 3 to 6 ring carbon atoms wherein the cycloalkyl  
 is unsubstituted or one or two ring carbons are independently mono-  
 substituted by methyl or ethyl; or  
 a 5 or 6 membered heteroaromatic ring having 1 or 2 ring heteroatoms  
 selected from N, S and O and the heteroaromatic ring is covalently bound  
 to the remainder of the compound by a ring carbon,

comprising,

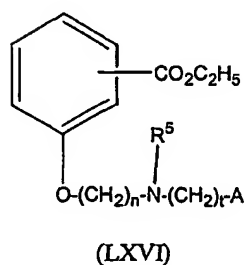
- a) reacting a compound of the formula:



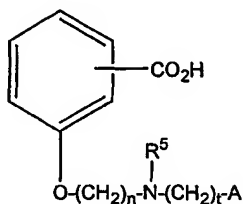
with a compound of the formula:



wherein  $\text{Y}^1$  is halo, and  $\text{R}^5$ ,  $n$ , and  $t$  are as above,  
 to yield the corresponding compound of the formula:

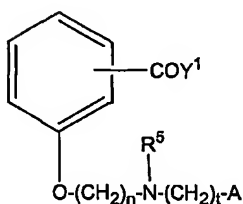


- b) hydrolyzing the compound of formula LXVI to yield the corresponding compound of the formula:



(LXVII)

- c) reacting the compound of formula LXVII with thionyl chloride to yield the corresponding compound of the formula:

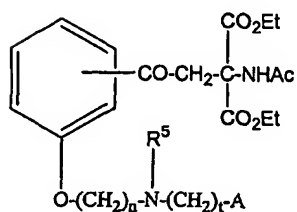


(LXVIII)

wherein Y<sup>1</sup> is chloro

- d) treating EtO<sub>2</sub>CH<sub>2</sub>COOH with about two equivalents of butyllithium; and
- e) reacting the compound of formula LXVIII with the product resulting from step d), to yield the compound of formula LXIX.

134. A process for producing a compound of the formula:



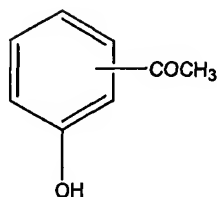
(LXXI)

wherein  $R^5$  is alkyl having from 1 to 3 carbon atoms; n is 1 or 2; t is 0 or 1; and

A is phenyl, unsubstituted or substituted by 1 or 2 groups selected from:  
halo, alkyl having 1 or 2 carbon atoms, perfluoromethyl, alkoxy having 1 or 2 carbon atoms, and perfluoromethoxy; or  
cycloalkyl having from 3 to 6 ring carbon atoms wherein the cycloalkyl is unsubstituted or one or two ring carbons are independently mono-substituted by methyl or ethyl; or  
a 5 or 6 membered heteroaromatic ring having 1 or 2 ring heteroatoms selected from N, S and O and the heteroaromatic ring is covalently bound to the remainder of the compound by a ring carbon,

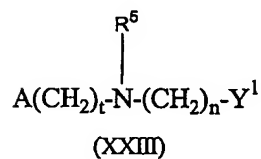
comprising,

a) reacting a compound of the formula:

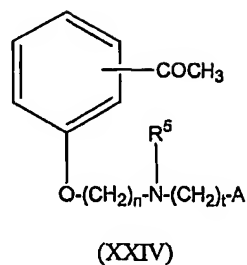


(VI)

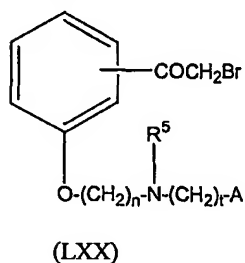
with a compound of the formula:



wherein  $Y^1$  is halo, and  $R^5$ , n, t and A are as above,  
to yield the corresponding compound of the formula:

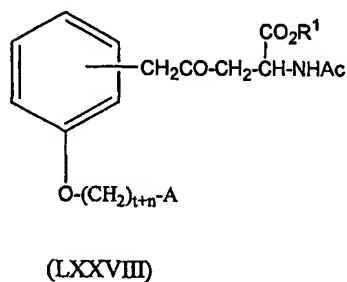


- b) treating the compound of formula XXIV with  $\text{CuBr}_2$  under selective bromination conditions to yield the compound of the formula:



- c) reacting the compound of formula LXX with the sodium salt of diethylacetamidomalonate to yield the compound of formula LXXI.

135. A process for producing a compound of the formula:



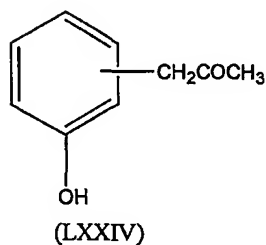
wherein  $\text{R}^1$  is hydrogen; n is 1 or 2; t is 0 or 1; and

- A is phenyl, unsubstituted or substituted by 1 or 2 groups selected from: halo, alkyl having 1 or 2 carbon atoms, perfluoromethyl, alkoxy having 1 or 2 carbon atoms, and perfluoromethoxy; or cycloalkyl having from 3 to 6 ring carbon atoms wherein the cycloalkyl is unsubstituted or one or two ring carbons are independently mono-substituted by methyl or ethyl; or

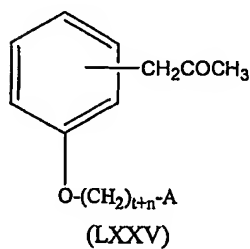
a 5 or 6 membered heteroaromatic ring having 1 or 2 ring heteroatoms selected from N, S and O and the heteroaromatic ring is covalently bound to the remainder of the compound by a ring carbon,

comprising,

a) reacting a compound of the formula:

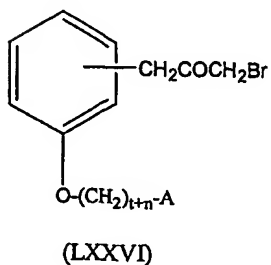


with either: i) a compound of formula  $A(CH_2)_{t+n}-OH$  under Mitsunobu conditions, or ii) a compound of formula  $A(CH_2)_{t+n}-Y$ , to yield the corresponding compound of the formula:

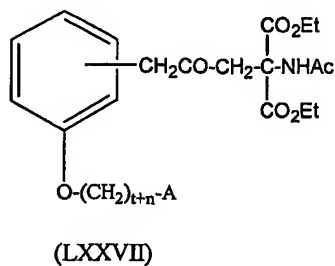


wherein n, t and A are as above and Y is a leaving group

b) reacting the compound of formula LXXV with HBr to yield the corresponding compound of the formula:

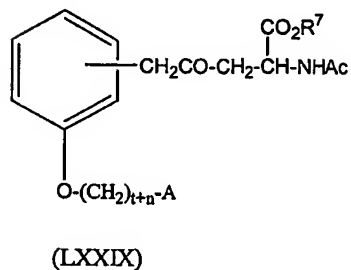


- c) reacting the compound of formula LXXVI with the sodium salt of diethylacetamidomalonate to yield the corresponding compound of formula



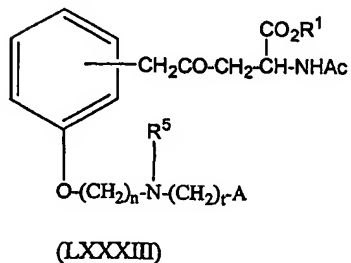
- d) deesterifying the compound of formula LXXVII to yield the compound of formula LXXVIII.

136. The process of claim 135, further comprising reacting the compound of formula LXXVIII with  $R^7$ -OH, wherein  $R^7$  is alkyl having from 1 to 7 carbon atoms, to yield the corresponding compound of the formula:



wherein n, t,  $R^7$  and A are as above.

137. A process for producing a compound of the formula:



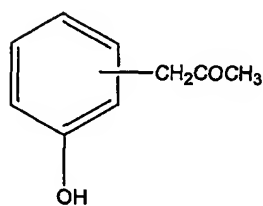


wherein  $R^1$  is hydrogen;  $R^5$  is alkyl having from 1 to 3 carbon atoms;  $n$  is 1 or 2;  $t$  is 0 or 1; and

- A is phenyl, unsubstituted or substituted by 1 or 2 groups selected from: halo, alkyl having 1 or 2 carbon atoms, perfluoromethyl, alkoxy having 1 or 2 carbon atoms, and perfluoromethoxy; or cycloalkyl having from 3 to 6 ring carbon atoms wherein the cycloalkyl is unsubstituted or one or two ring carbons are independently mono-substituted by methyl or ethyl; or a 5 or 6 membered heteroaromatic ring having 1 or 2 ring heteroatoms selected from N, S and O and the heteroaromatic ring is covalently bound to the remainder of the compound by a ring carbon,

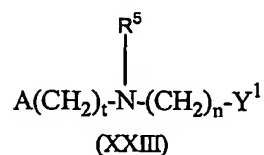
comprising,

- a) reacting a compound of the formula:

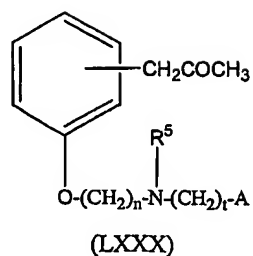


(LXXIV)

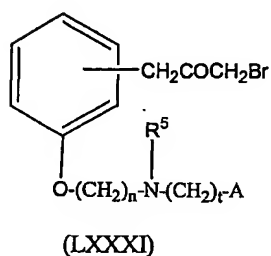
with a compound of the formula:



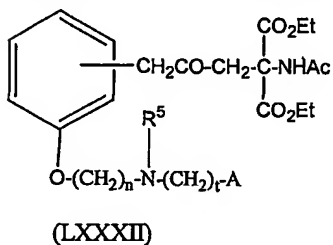
wherein  $R^5$ ,  $n$ ,  $t$  and  $A$  are as above and  $Y^1$  is chloro, to yield the corresponding compound of the formula:



- b) reacting the compound of formula LXXX with HBr to yield the corresponding compound of the formula:

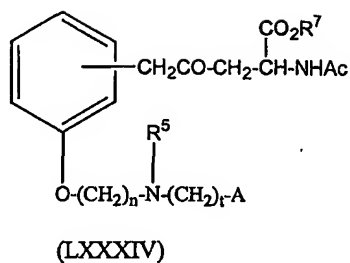


- c) reacting the compound of formula LXXXI with the sodium salt of diethylacetamidomalonate to yield the corresponding compound of formula



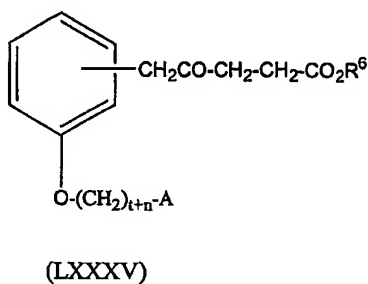
- d) deesterifying the compound of formula LXXXII to yield the compound of formula LXXXIII.

138. The process of claim 137, further comprising reacting the compound of formula LXXXIII with  $R^7$ -OH, wherein  $R^7$  is alkyl having from 1 to 7 carbon atoms, to yield the corresponding compound of the formula:



wherein n, t, R<sup>5</sup>, R<sup>7</sup> and A are as above.

139. A process for producing a compound of the formula:

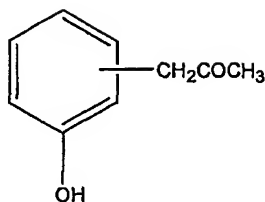


wherein R<sup>6</sup> is alkyl having from 1 to 7 carbon atoms; n is 1 or 2; t is 0 or 1; and

A is phenyl, unsubstituted or substituted by 1 or 2 groups selected from:  
 halo, alkyl having 1 or 2 carbon atoms, perfluoromethyl, alkoxy having 1 or 2 carbon atoms, and perfluoromethoxy; or  
 cycloalkyl having from 3 to 6 ring carbon atoms wherein the cycloalkyl is unsubstituted or one or two ring carbons are independently mono-substituted by methyl or ethyl; or  
 a 5 or 6 membered heteroaromatic ring having 1 or 2 ring heteroatoms selected from N, S and O and the heteroaromatic ring is covalently bound to the remainder of the compound by a ring carbon,

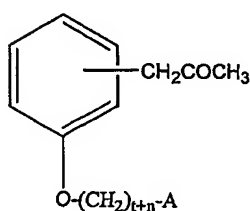
comprising,

a) reacting a compound of the formula:



(LXXIV)

with either: i) a compound of formula  $A(CH_2)_{t+n}-OH$  under Mitsunobu conditions, or ii) a compound of formula  $A(CH_2)_{t+n}-Y$ , to yield the corresponding compound of the formula:



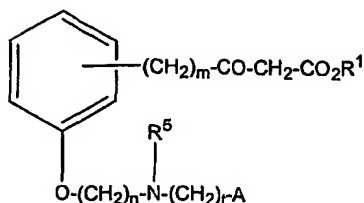
(LXXV)

wherein  $n$ ,  $t$  and  $A$  are as above and  $Y$  is a leaving group

b) reacting the compound of formula LXXV with  $Br-CH_2-CO_2R^6$ , wherein  $R^6$  is as above, to yield the compound of formula LXXXV.

140. The process of claim 139, further comprising deesterifying the compound of formula LXXXV to remove  $R^6$  and yield the corresponding acid.

141. A process for producing the compound of the formula:



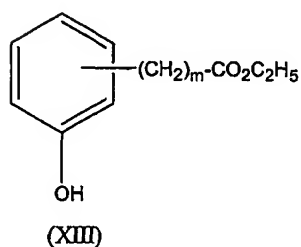
(LXXXIX)

wherein  $R^1$  is ethyl,  $R^5$  is alkyl having from 1 to 3 carbon atoms;  $m$  is 1;  $n$  is 1 or 2;  $t$  is 0 or 1; and

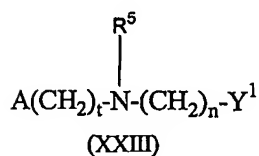
- A is phenyl, unsubstituted or substituted by 1 or 2 groups selected from:  
 halo, alkyl having 1 or 2 carbon atoms, perfluoromethyl, alkoxy having 1 or 2 carbon atoms, and perfluoromethoxy; or  
 cycloalkyl having from 3 to 6 ring carbon atoms wherein the cycloalkyl is unsubstituted or one or two ring carbons are independently mono-substituted by methyl or ethyl; or  
 a 5 or 6 membered heteroaromatic ring having 1 or 2 ring heteroatoms selected from N, S and O and the heteroaromatic ring is covalently bound to the remainder of the compound by a ring carbon,

comprising

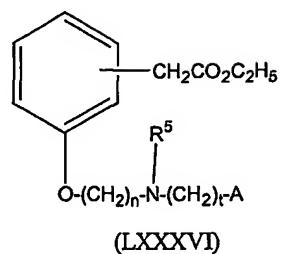
- a) reacting a compound of the formula:



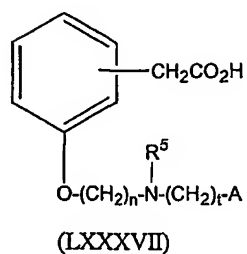
with a compound of the formula:



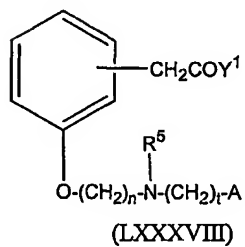
wherein  $\text{Y}^1$  is chloro and  $m$ ,  $n$ ,  $t$ ,  $\text{R}^5$  and  $\text{A}$  are as above, to yield the corresponding compound of the formula:



- b) hydrolyzing the compound of formula LXXXVI to yield the corresponding compound of the formula:



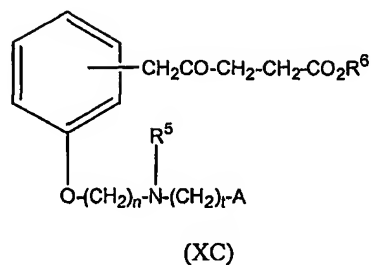
- c) reacting the compound of formula LXXXVII with thionyl chloride to yield the corresponding compound of the formula:



wherein Y<sup>1</sup> is chloro

- d) reacting the acid halide with Meldrum acid to yield the compound of formula LXXXIX.

142. A process for producing the compound of the formula:

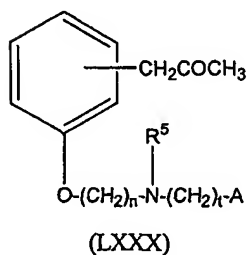


wherein  $R^5$  is alkyl having from 1 to 3 carbon atoms;  $R^6$  is alkyl having from 1 to 7 carbon atoms;  $n$  is 1 or 2;  $t$  is 0 or 1; and

A is phenyl, unsubstituted or substituted by 1 or 2 groups selected from: halo, alkyl having 1 or 2 carbon atoms, perfluoromethyl, alkoxy having 1 or 2 carbon atoms, and perfluoromethoxy; or cycloalkyl having from 3 to 6 ring carbon atoms wherein the cycloalkyl is unsubstituted or one or two ring carbons are independently mono-substituted by methyl or ethyl; or a 5 or 6 membered heteroaromatic ring having 1 or 2 ring heteroatoms selected from N, S and O and the heteroaromatic ring is covalently bound to the remainder of the compound by a ring carbon,

comprising

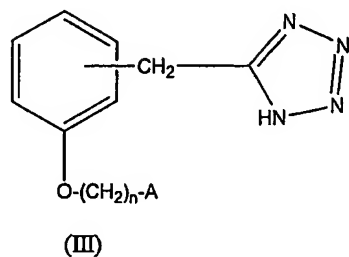
a) reacting a compound of the formula:



with  $\text{Br-CH}_2\text{-CO}_2\text{R}^6$ , wherein  $R^5$ ,  $R^6$ ,  $n$ ,  $t$  and A are as above, to yield the compound of formula XC.

143. The process of claim 141, further comprising deesterifying the compound of formula XC to remove  $R^6$  and yield the corresponding acid.

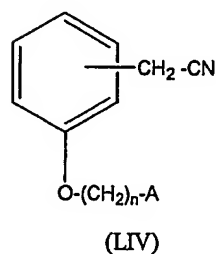
144. A process for producing a compound of the formula:



wherein n is 1 or 2; and

A is phenyl, unsubstituted or substituted by 1 or 2 groups selected from: halo, alkyl having 1 or 2 carbon atoms, perfluoromethyl, alkoxy having 1 or 2 carbon atoms, and perfluoromethoxy; or cycloalkyl having from 3 to 6 ring carbon atoms wherein the cycloalkyl is unsubstituted or one or two ring carbons are independently mono-substituted by methyl or ethyl; or a 5 or 6 membered heteroaromatic ring having 1 or 2 ring heteroatoms selected from N, S and O and the heteroaromatic ring is covalently bound to the remainder of the compound by a ring carbon,

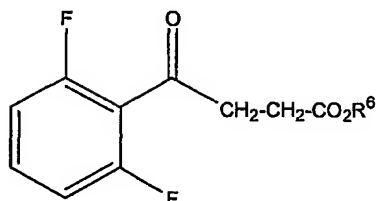
comprising reacting a compound of the formula:



wherein n and A are as above, with sodium azide in the presence of ammonium chloride in dimethylformamide to yield the corresponding compound of formula III.



145. A process for producing a compound of the formula:



(LVI)

wherein  $R^6$  is alkyl having from 1 to 7 carbon atoms comprising reacting 2',6'-difluoroacetophenone with  $Br-CH_2-CO_2R^6$ , wherein  $R^6$  is as above, to yield the compound of formula LVI.

146. The process of claim 145, further comprising deesterifying the compound of formula LVI to remove  $R^6$  and yield the corresponding acid.

147. Use of the biologically active agent of any one of claims 1 to 98 in the manufacture of a medicament for treatment of a condition selected from the group consisting of insulin resistance syndrome and diabetes including Type I Diabetes and Type II Diabetes; or for the treatment or reduction in the chance of developing atherosclerosis, arteriosclerosis, obesity, hypertension, hyperlipidemia, fatty liver disease, nephropathy, neuropathy, retinopathy, foot ulceration or cataracts associated with diabetes; or for the treatment of a condition selected from the group consisting of hyperlipidemia, cachexia, and obesity.

148. The use of claim 147, wherein the agent is selected from the group consisting of:

- 4-(4-(2-Fluorobenzyloxy)phenyl)-4-oxobutyric acid;
- 4-(4-(2-Methoxybenzyloxy)phenyl)-4-oxobutyric acid;
- 3-[(4-(2-Fluorobenzyloxy)phenyl)-methylthio]propionic acid;
- 4-(4-(3-Fluorobenzyloxy)phenyl)-4-oxobutyric acid;
- 4-(4-(4-Fluorobenzyloxy)phenyl)-4-oxobutyric acid;

4-(4-((2-Pyridinyl)-methoxy)phenyl)-4-oxobutyric acid;  
4-(4-(Benzyloxy)phenyl)-4-oxobutyric acid;  
4-(4-(2,6-Difluorobenzyloxy)phenyl)-4-oxobutyric acid;  
4-(4-(2-Chlorobenzyloxy)phenyl)-4-oxobutyric acid;  
4-(4-(2-(2-Fluorophenyl)ethoxy)phenyl)-4-oxobutyric acid;  
Ethyl 4-(4-(2-fluorobenzyloxy)phenyl)-4-oxobutyrate;  
4-(4-(2-Methylbenzyloxy)phenyl)-4-oxobutyric acid;  
4-[4-(2-(N-(2-fluorobenzyl)-N-methylamino)ethoxy)phenyl]-4-oxobutyric acid;  
4-(3-(2-Methylbenzyloxy)phenyl)-4-oxobutyric acid;  
Ethyl 4-(3-(2-fluorobenzyloxy)phenyl)-4-oxobutyrate;  
Ethyl 4-(4-(2-methylbenzyloxy)phenyl)-4-oxobutyrate;  
Ethyl 4-(4-(2,6-difluorobenzyloxy)phenyl)-4-oxobutyrate;  
4-(4-(2-(2-Thienyl)ethoxy)phenyl)-4-oxobutyric acid;  
4-(2,6-Difluorophenyl)-4-oxobutyric acid;  
4-(4-(2,5-Dimethylbenzyloxy)phenyl)-4-oxobutyric acid;  
4-(4-(2,5-Difluorobenzyloxy)phenyl)-4-oxobutyric acid;  
4-(4-(2,4-Difluorobenzyloxy)phenyl)-4-oxobutyric acid;  
4-(3-(2,6-Difluorobenzyloxy)phenyl)-4-oxobutyric acid;  
4-(4-((Cyclopropyl)-methoxy)phenyl)-4-oxobutyric acid;  
4-(4-(2-Trifluoromethylbenzyloxy)phenyl)-4-oxobutyric acid;  
3-[(4-(2,6-Difluorobenzyloxy)phenyl)-methylthio]propionic acid;  
4-(2-(2,6-Difluorobenzyloxy)phenyl)-4-oxobutyric acid;  
Ethyl 4-(4-(2,6-difluorobenzyloxy)phenyl)methyl-3-oxobutyrate;  
3-(2-(4-(2,6-Difluorobenzyloxy)phenyl)-2-oxoethyl)thio-(1H-1,2,4)-triazole;  
5-[(4-(2,6-Difluorobenzyloxy)phenyl)-methyl]-1H-tetrazole;  
(2RS) 2-(N-Boc)-3-[2-(4-(2,6-difluorobenzyloxy)phenyl)-2-oxoethyl]  
thiopropionic acid;  
Ethyl 2-Hydroxy-4-oxo-4-(4-(2,6-difluorobenzyloxy)phenyl) but-2-enoate;  
(2RS) 2-(N-Acetyl)-4-(4-(2,6-difluorobenzyloxy)phenyl)-4-oxobutyric acid;  
4-(3-((Cyclopropyl)-methoxy)phenyl)-4-oxobutyric acid;  
4-(3-(2,6-Dimethylbenzyloxy)phenyl)-4-oxobutyric acid;  
4-(3-(2-Fluoro-6-methylbenzyloxy)phenyl)-4-oxobutyric acid;  
Ethyl 4-(3-(2,6-dimethylbenzyloxy)phenyl)-4-oxobutyrate;  
4-(3-(2,6-Dimethylbenzyloxy)phenyl)-4-oxobutyric acid Sodium salt;

4-(4-(2,6-Dimethylbenzyloxy)phenyl)-4-oxobutyric acid;  
4-(3-(2,6-Dimethylbenzyloxy)phenyl)-4-oxobutyric acid Potassium salt;  
4-(3-(2,6-Dimethoxybenzyloxy)phenyl)-4-oxobutyric acid;  
4-(3-(2,6-Dimethylbenzyloxy)phenyl)-4-oxo-2,2-dimethylbutyric acid;  
4-(3-(4-Trifluoromethylbenzyloxy)phenyl)-4-oxobutyric acid;  
4-(3-((Cyclobutyl)-methoxy)phenyl)-4-oxobutyric acid;  
4-(3-(2,6-Dimethylbenzyloxy)phenyl)butyric acid;  
4-[[4-(2,6-Dimethylbenzyloxy)-3-methoxy]phenyl]-4-oxobutyric acid;  
4-[5-[[N-(4-Trifluoromethylbenzyl)aminocarbonyl]-2-methoxy]phenyl]-4-oxobutyric acid;  
4-[5-[[N-(2,6-Dimethylbenzyl)aminocarbonyl]-2-methoxy]phenyl]-4-oxobutyric acid;  
4-(3-(2,6-Dimethylbenzyloxy)phenyl)-4-oxobutanecarbohydroxamic acid;  
4-(3-(2,6-Dimethylbenzyloxy)phenyl)-4-oxobutyramide;  
4-(3-(2,6-Dimethylbenzyloxy)phenyl)-4-oxo-2-butenic acid; and  
4-(3-(2,6-Dimethylbenzyloxy)phenyl)-3-butenic acid.

149. The use of claim 148, wherein the agent is 4-(4-(2,6-difluorobenzyloxy)phenyl)-4-oxobutyric acid.

150. The use of claim 148, wherein the agent is 4-(3-(2,6-difluorobenzyloxy)phenyl)-4-oxobutyric acid.

151. The use of claim 148, wherein the agent is 4-(3-(2,6-dimethylbenzyloxy)phenyl)-4-oxobutyric acid.

152. The use of any one of claims 147 to 151, wherein the medicament is formulated for oral administration.

153. A method for treating a mammalian subject with a condition selected from the group consisting of insulin resistance syndrome, diabetes, hyperlipidemia, fatty liver disease, cachexia, obesity, atherosclerosis and arteriosclerosis comprising administering to the subject an amount of the

biologically active agent of any one of claims 1 to 98 effective to treat the condition.

154. The method of claim 153, wherein the agent is administered orally.

155. The method of claim 153, wherein the subject is a human.

156. The method of claim 155, wherein the agent is administered in an amount from one milligram to four hundred milligrams per day.

157. The method of claim 153, wherein the condition is insulin resistance syndrome or Type II Diabetes.

158. The method of claim 153, wherein the condition is Type 1 Diabetes.

159. The method of claim 153, wherein the treatment reduces a symptom of diabetes or the chances of developing a symptom of diabetes, wherein the symptom is selected from the group consisting of: atherosclerosis, obesity, hypertension, hyperlipidemia, fatty liver disease, nephropathy, neuropathy, retinopathy, foot ulceration and cataracts, associated with diabetes.

160. A pharmaceutical composition for use in the treatment of a condition selected from the group consisting of insulin resistance syndrome, diabetes, hyperlipidemia, fatty liver disease, cachexia, obesity, atherosclerosis, arteriosclerosis and adapted for oral administration, comprising from one milligram to four hundred milligrams of the agent of any one of claims 1 to 98.

161. The invention substantially as described above.

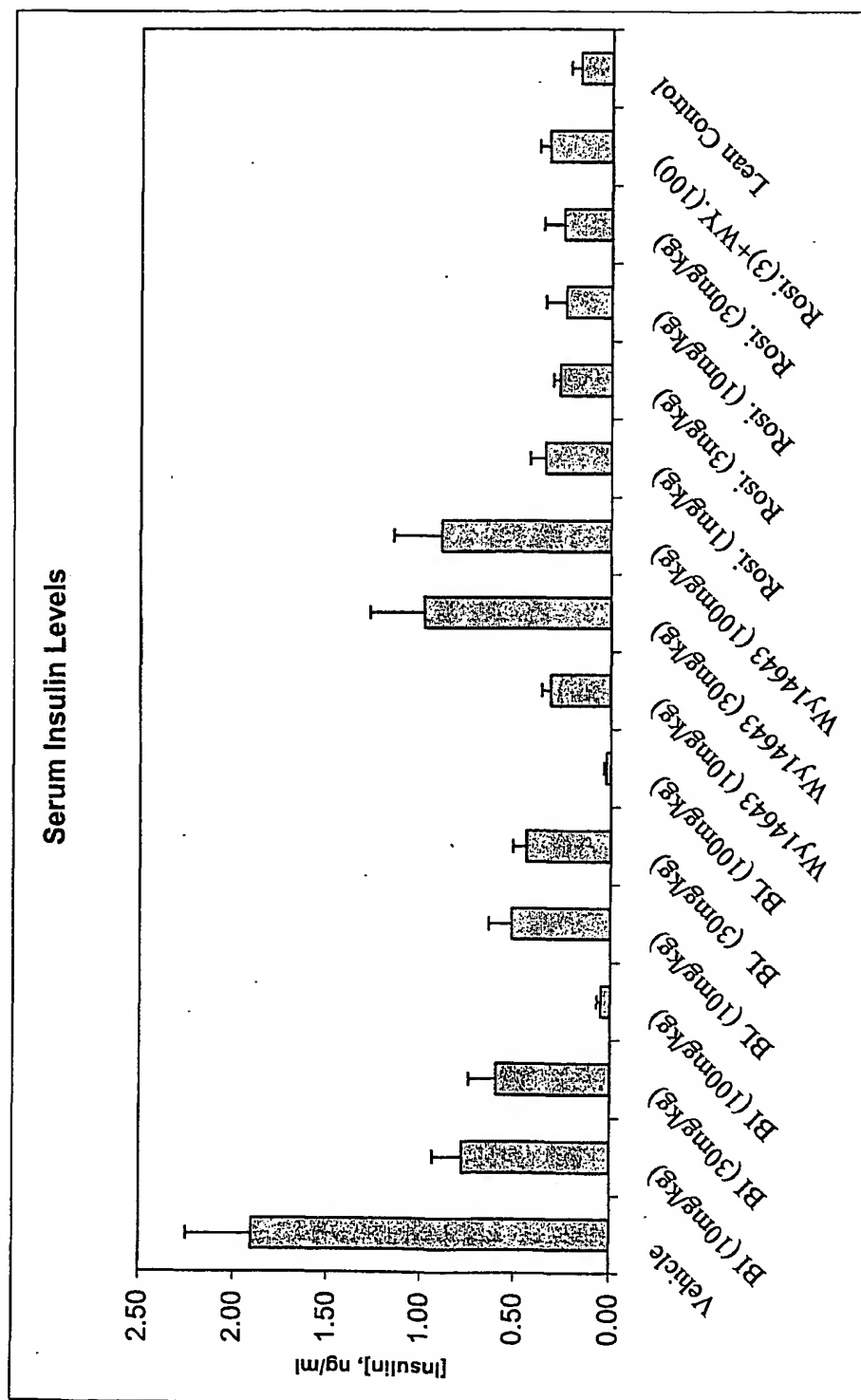


FIGURE 1  
1/2

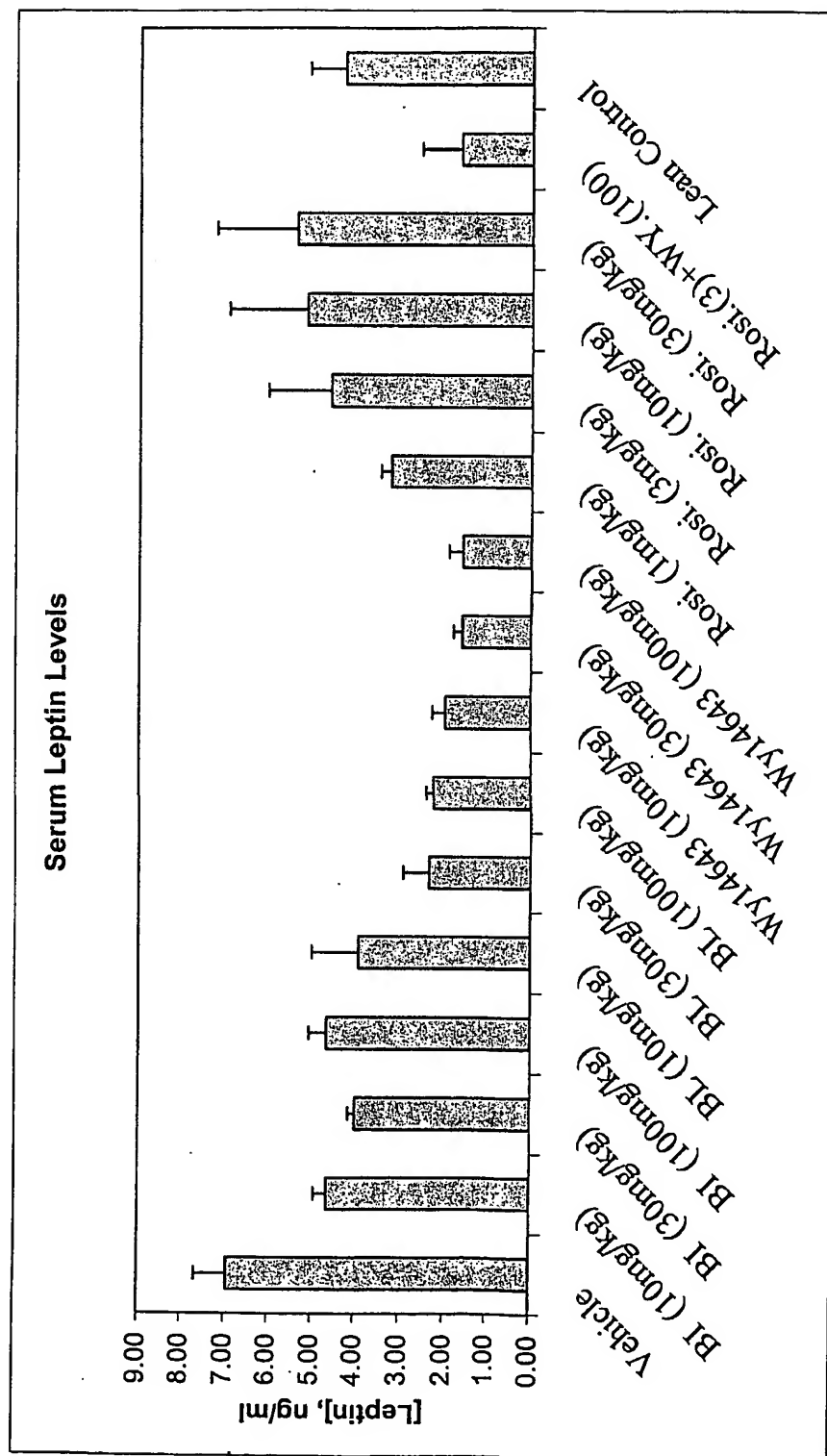


FIGURE 2

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/18388

<b>A. CLASSIFICATION OF SUBJECT MATTER</b>		
IPC(7) : C07D 249/12, 257/00; C07C 69/76, 59/86, 59/90, 229/00		
US CL : 548/253, 264.4; 560/37, 53; 562/451, 456, 459, 463		
According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b>		
Minimum documentation searched (classification system followed by classification symbols) U.S. : 548/253, 264.4; 560/37, 53; 562/451, 456, 459, 463		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) Please See Continuation Sheet		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99/20275 A1 (RHONE-POULENC RORER PHARMACEUTICALS INC.) 22 April 1999 (22.04.1999), page 27.	80, 161
A	WITIAK et al. Synthesis of Ethyl 6-Substituted-Chroman- and Chromone-2-carboxylates. A Comparative Structure-Activity Study Employing the 6-Phenyl and Phenoxy Analogs in the Triton Hyperlipidemic Rat Model. Journal Medicinal Chemistry. 1975, Vol. 18, No. 5, pages 934-942, page 935, bottom, compound 40.	86-89, 161
X	WO 99/11255 A1 (ONO PHARMACEUTICAL CO., LTD.) 11 March 1999 (11.03.1999), page 32, compound 1.	94, 161
---		95
A		
X	US 4,098,816 A (THORNE et al.) 04 July 1978 (07.04.1978), columns 1-12, lines 1-55, entry 1, column 14, lines 23-68. column 19, lines 20-50.	94, 99-101, 106-107, 153-161
X	US 4,638,094 A (NAKAI et al.) 20 January 1987 (20.01.1987), column 19, Table 12, example no. 85.	115, 161
X	DE 2 309 986 A1 (GHELARDONI et al.) 29 August 1974 (29.08.1974), see CAS abstract, lines 1-3.	108, 161
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.		
* Special categories of cited documents:		
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"
"E"	earlier application or patent published on or after the international filing date	"Y"
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"
"O"	document referring to an oral disclosure, use, exhibition or other means	
"P"	document published prior to the international filing date but later than the priority date claimed	
Date of the actual completion of the international search		Date of mailing of the international search report
06 February 2004 (06.02.2004)		17 MAY 2004
Name and mailing address of the ISA/US		Authorized officer
Mail Stop PCT, Attn: ISA/US		Paul A. Zucker
Commissioner for Patents		
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Facsimile No. (703)305-3230		

# INTERNATIONAL SEARCH REPORT

PCT/US02/18388

## C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 01/40170 A1 (ASTRAZENECA AB) 07 June 2001 (07.06.2001), entire document.	1-79, 86-95, 99-101, 153-161
E, X	US 6,555,536 B2 (BURRIS et al.) 29 April 2003 (29.04.2003), column 37, lines 25-40.	80, 153-161



# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/18388

## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claim Nos.: 147-152  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:  
Use claims do set forth positive method steps as required.
3. ☒ Claim Nos.: 152  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

PCT/US02/18388

**Continuation of B. FIELDS SEARCHED Item 3:**

CAS ONLINE

search terms: strucures, diabete?, diabet?